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ORIGINAL ARTICLES

STUDIES IN ATOPIC DERMATITIS

V. Problems in Inhalant Hyposensitization and Results of Treatment

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IN PREVIOUS studies my associates and I conclusively demonstrated that such inhalant allergens as house dust, pollens, and/or molds were important causes of atopic dermatitis.[1-4] We were able to induce the dermatitis in susceptible subjects both by the inhalation of powdered house dust, alternaria, and ragweed pollen and by the injection of extracts of these allergens.

The demonstration of the etiological importance of inhalant allergens focused attention upon the question of hyposensitization with extracts of these allergens. Contact with inhalant allergens is neither easily nor completely avoided, even though the amount of exposure to them may be somewhat reduced; hence, proper treatment in these patients, as in asthmatic patients allergic to similar inhalants, must include attempts at hyposensitization with extracts of the offending inhalants. This method had been employed to some extent by both allergists and dermatologists but, judging from sporadic reports in the literature, not with any consistent degree of success.

The literature pertaining to the effect of hyposensitizing treatment in atopic dermatitis is scant. Prior to our own publications relating to the management of this condition, only occasional mention was made of the use of extracts of house dust or pollen in treatment. For example, in 1946 Rowe[5] reported instances of atopic dermatitis of the hands due to plant pollen and discussed in a general way the use of hyposensitizing injections with pollen extracts. None of the previous articles, however, included details of the methods used or of the end results of treatment. Since the publication of our own studies, Diamond[6] also reported on the value of hyposensitization with inhalant allergens.

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Undoubtedly, those physicians who first see these patients (for example, allergists, dermatologists, and pediatricians) have attempted to employ hyposensitization, especially with house dust extract, in selected cases but apparently without consistent success. Thus, Nexmand,[7] in a monograph on this subject published in 1948, finally concludes both from his own experience and from a review of an extensive amount of literature on atopic dermatitis that "this method of treatment (hyposensitization) is not generally recommended for Besnier's prurigo" (atopic dermatitis). That Nexmand should have come to such a conclusion is not surprising since, up until the time of his publication in 1948, the significance of inhalants as a cause of atopic dermatitis remained, at best, a clinical suspicion. Now that our studies have directed attention to the inhalant allergens as important causes, however, more opportunities have arisen to utilize hyposensitization with extracts of house dust, pollens, or molds in the treatment of these patients. This has been true in our experience especially in the past ten years, during which time we have had an opportunity to treat a larger number of patients with extracts of inhalant allergens. During this period, as the result of the institution of treatment with these extracts, we encountered some unexpected problems and experiences which perhaps serve to explain some of the previous treatment failures, both our own and those of others. We also learned many lessons, sometimes at the expense of the patient's comfort, which were helpful in our treatment of subsequent patients. These experiences form the basis of the present report, and it is my hope that they might assist others in the treatment of patients with atopic dermatitis.

TABLE I. SUMMARY OF 183 PATIENTS WITH ATOPIC DERMATITIS*

Atopic dermatitis as chief complaint	137		
Allergic manifestations			
Atopic dermatitis only		34	
And hay fever		29	
And asthma		43	
Asthma and hay fever		60	
Other allergies		17	
Number of patients treated by diet only			18
Number of patients treated by hyposensitization			125
Number of patients who did not return			40

*All but fifteen patients were from the author's private practice.

The series of patients reviewed for this report comprise a total of 183 patients, most of whom were from my private practice (Table I). Of these, 137 were seen primarily because of atopic dermatitis and forty-six primarily for other allergic complaints (hay fever and asthma, among others). Most of the patients had more than one allergic condition at the time they were first seen; thus, only thirty-four had atopic dermatitis alone. Of the 183 patients, forty either did not return or went back to the referring physician for follow-up treatment and eighteen were treated solely by dietary exclusion. This leaves 125 patients, eighty-two of whom were treated since 1949, the date of my first publication concerning the role of inhalant allergens. The general

plan of treatment followed closely that usually used in cases of asthma. All patients had complete allergy studies, which included intracutaneous skin tests with extracts of food allergens and with seasonal and nonseasonal inhalant allergens. The patient then was given a list of the positive-reacting allergens with instructions as to their avoidance or, in the case of house dust, the methods by which exposure to it could be minimized. In patients in whom sensitivity to pollens or molds could be established as etiological factors (either by clinical history or by testing), or in dust-sensitive patients for whom complete avoidance was difficult, hyposensitization treatment with the extracts of these allergens was instituted. Of the 125 patients (Table II), 107 were treated with house dust extract, seventy-eight with ragweed pollen extract, forty-three with the extract of a spring pollen mixture containing timothy and plantain—and five with alternaria (either alone or mixed with hormodendrum). In thirty-five patients who were sensitive both to ragweed and to the latter molds, the mold extracts usually were combined with the ragweed extract in a single vial and used in treatment. Patients sensitive to more than one allergen were treated whenever necessary with more than one extract, for example, house dust and ragweed or house dust and ragweed mold. This was true in all but fourteen of the 125 patients.

TABLE II. SUMMARY OF EXTRACTS USED

House dust	107
Ragweed pollen	78
Mixture of timothy, plantain, and sweet vernal	43
Mixture of alternaria and hormodendrum molds	5
Mixture of ragweed (giant and dwarf) and alternaria	35

Among the first of the patients treated with dust extract was a 62-year-old man who was first seen by me in 1939 because of fall hay fever of many years' duration and severe generalized atopic dermatitis which had begun in November, 1938. This cleared after hospitalization but recurred upon his return home. The clinical suspicion that he was sensitive to his own environmental house dust was substantiated by specific positive skin reactions and specific reagins to an autogenous house dust extract. Treatment with the latter and with ragweed pollen extract was instituted on a perennial basis. The hyposensitization treatment, which was given in the same manner as to an asthmatic patient, began with a small dose of the extract which was increased gradually until the maximum tolerated dose was being given. No difficulties were encountered in the administration of these extracts; in fact, the patient was able to tolerate the concentrated autogenous dust extract and a large dose of ragweed pollen extract (see Patient M. in Table IV) without reaction. Excellent clinical results were obtained, and after three years treatment was discontinued. We last heard from this patient in 1949, when he stated that up to that time he had not had any recurrence of the dermatitis and his hay fever was considerably improved.

Following this experience, I treated other atopic dermatitis patients in similar fashion, but not always with the same success. For example, in several

patients receiving hyposensitizing injections of allergenic extracts temporary improvement of the dermatitis would follow institution of this treatment, but after a while unexplained relapses would occur and not infrequently the treatment would be discontinued by the patient. We puzzled at length about this situation until the reason became evident following our experimental clinical studies first reported in 1950.[2] In the patient used for most of these studies (Patient M. B. in Table V), after our attempted hyposensitization was begun, we encountered an exquisite degree of sensitiveness to an extent not previously anticipated. Reactions could be induced from almost infinitesimal amounts of extract. Furthermore, in contrast to the immediate form of reaction sometimes observed in hay fever patients receiving pollen hyposensitization, the reaction in the atopic dermatitis patient was so delayed that it could be easily overlooked. The patient utilized for these studies was a 29-year-old male veteran first seen in 1948 because of an extensive generalized atopic dermatitis for which he had been hospitalized on several occasions. Clinical observation, as well as direct and indirect skin testing, revealed specific reaginic sensitivity especially to house dust, both autogenous and stock. Subsequently, we were able to demonstrate that the atopic dermatitis could be induced repeatedly in him both by the inhalation of micronized particles of house dust and/or of alternaria and also, on five separate occasions, by intracutaneous injection of the concentrated autogenous dust extract. By contrast, as a control, inhalation of talc or of timothy pollen (to which he was not allergic) and intracutaneous injection of timothy pollen extract in high concentration failed to induce the lesions of his atopic dermatitis. As part of his treatment, we began a program of hyposensitization with extracts of autogenous house dust and with a mixture of ragweed and alternaria extracts, but we soon encountered unexpected difficulties. Injection of unbelievably minute doses of the pollen-mold extract was followed by an exacerbation of the dermatitis, similar to that originally induced by injection of larger amounts. In order to exclude any extraneous factors as possible causes of the exacerbation, we repeatedly, and without the patient's knowledge, substituted either buffered saline, the diluent employed for the preparation of these extracts, or at times timothy pollen extract (0.1 N strength) to which he was not sensitive. When the latter solutions were used, no increase in symptoms followed, whereas the reintroduction of the specific extract produced a definite reaction. The extracts then were diluted progressively to reach a dilution and a dose which no longer induced a reaction. The safe dosage finally was ascertained to be ragweed and alternaria 0.000003 N. This experience was duplicated in the patient frequently enough to warrant the conclusion that the reaction must have been the result of the injection of the minute amount of the allergenic extract. In all instances, the reactions did not take place immediately but after a lapse of twelve to twenty hours or longer.

This experience made us more aware of the possibility that reactions from hyposensitizing injections might be delayed in onset and might follow an

extremely small dosage. We therefore began to be much more careful with the dosage in treating subsequent patients and were alerted for delayed reactions.

Of the 125 patients who were given hyposensitizing injections of various allergenic extracts, thirty-four patients had a total of forty-nine reactions. As shown in Table III, five patients had reactions following testing procedures. In two, there was an exacerbation of the dermatitis after testing with concentrated autogenous house dust extracts; one followed testing with ragweed (0.1 N) and two followed tests (twelve or more) with routine allergens. In four patients, the reactions were deliberately induced for experimental reasons —in one patient by administration of dust extract and in three others by injection of ragweed extract. Twenty-eight patients had a total of thirty-nine reactions which were not intentionally induced but followed hyposensitizing injections of allergenic extracts. Some patients had more than one reaction, either because we did not realize at first that the reaction was induced by the injection or because the injection was repeated to make sure that it was responsible for the reaction. Most of the reactions followed the injection of either house dust extract (seventeen) or of ragweed extract (thirteen), but this was because these extracts were employed in treatment more frequently than other extracts (Table II).

TABLE III. REACTIONS IN ATOPIC DERMATITIS PATIENTS

INDUCED BY	MULTIPLE TESTS	HOUSE DUST	RAGWEED (GIANT AND DWARF)	RAGWEED AND ALTERNARIA	ALTERNARIA	GRASS MIXTURE*	TOTAL REACTIONS	NUMBER OF PATIENTS
Tests	2	2	1				5	5
Treatment		17	13	5	2	2	39	28
Experimental induction		1	3		1		5	4

*Grass mixture contains timonthy, plantain, and sweet vernal.

The reactions which followed hyposensitizing injections, regardless of dosage, always were delayed in onset from twelve to twenty-four hours or longer. They would consist either of exacerbation of the existing dermatitis or the appearance of new papules, especially in the flexures, which resembled and at times were mistakenly diagnosed as "prickly heat." In most patients, the reaction would occur early in the course of treatment, either after the initial injection or after a few doses had been given. If a reaction did occur, the dose was altered in a manner similar to that employed in the hyposensitization treatment of other allergic diseases such as hay fever. Thus, the dosage would be decreased until no reaction occurred and subsequently increased more slowly until the maximum tolerated dose was reached without induction of reaction. By adopting this procedure, we found that most of our patients, even though they had reactions from one or more doses, were able later to tolerate larger dosages without difficulty. The maximum dosage reached in many patients compared favorably with that given to patients with hay fever or asthma. Some illustrative examples are contained in Table IV.

TABLE IV. ATOPIC DERMATITIS PATIENTS—ABLE TO TOLERATE LARGE DOSAGE

PATIENT	AGE	DIAGNOSIS	MAXIMUM TOLERATED DOSE
M.	62	Atopic dermatitis Hay fever	Ragweed 0.36 N Autogenous dust (c) 0.2 ml.
S. P.	10	Atopic dermatitis	Ragweed 0.18 N Grass mixture* 0.2 N
E. S.	21	Atopic dermatitis	Ragweed 0.36 N Autogenous dust (c) 0.2 ml.
E. M.	46	Atopic dermatitis Hay fever Asthma	Ragweed 0.24 N Grass and tree mixture 0.12 N Autogenous dust (c) 0.33 ml.
C. M.	40	Atopic dermatitis	Ragweed 0.18 N Dust (c) 0.1 ml. Plantain 0.08 N
P. S.	12	Atopic dermatitis Asthma	Ragweed 0.24 N Grass mixture 0.05 N Autogenous dust (c) 0.2 ml.

N = Total nitrogen.
(c) = Concentrate.
*Grass mixture contains timothy, plantain, and sweet vernal.

By contrast, however, in five of the 125 patients receiving treatment, reactions followed extremely minute amounts of extracts. Furthermore, even after repeated attempts, these patients could not tolerate any material increase in dosage. The data as to dosage tolerated by this group are summarized in Table V. Reactions in these patients followed extremely minute doses and recurred in most patients when the dosage was repeated. The reactions at times were so severe and incapacitating that further attempts at

TABLE V. ATOPIC DERMATITIS PATIENTS—REACTIONS FROM LOW DOSAGE

PATIENT	AGE	DIAGNOSIS	REACTION DOSAGE	SUBSEQUENT TOLERATED DOSE
S. B.	29	Atopic dermatitis	Autogenous dust (1:100,000) 0.05 ml. (i)	Autogenous dust (1:1 million) 0.1 ml. intracutaneous
D. G.	28	Atopic dermatitis Hay fever Asthma	Ragweed 0.0005 N Autogenous dust (1:10,000) 0.15 ml.	Ragweed and alternaria 0.0001 N—0.05 ml. Dust injection temporarily stopped
G. R.	24	Atopic dermatitis	Dust (1:10,000) 0.1 ml.	Dust (1:10,000) 0.05 ml.
M. B.	29	Atopic dermatitis	Ragweed and alternaria 0.000001 N	Ragweed and alternaria 0.000003 N
D. R.	36	Atopic dermatitis	Dust (1:1 million) 0.01 ml. (i)	Dust injection discontinued due to severe reaction

hyposensitizations were discontinued and only symptomatic treatment was instituted. This was true in Patients S.B., M.B., and D.R. Furthermore, because of the reaction induced by treatment and failure to respond, Patient G.R. discontinued further visits. Actually, of the five, we were able to continue treatment only in Patient D.G., in whom good results were obtained

eventually. As an illustration of the possible severity of the induced reactions, the case history of D.R. is worth citing.

D. R., a 36-year-old army veteran, was seen on Oct. 15, 1956, with an eczematous dermatitis of the trunk, hands, and feet which had been present since 1944. He had been treated by numerous dermatologists for "eczematous dermatitis" or "neurodermatitis" and had received various local applications without benefit. Allergy studies showed significant positive skin and eye test reactions to house dust and positive skin test reactions to a few foods of no clinical significance. Diet trial over an extended period failed to bring about improvement, and hyposensitization with stock house dust extract was begun. Severe reactions with eruption of lesions over the arms, face, and abdomen followed small doses of the extract diluted at first 1:100 and later 1:1,000. Because of the reaction, it was decided to give the injections intracutaneously. On two occasions 0.1 c.c. of a 1:1,000 extract was given intracutaneously, but in each instance it was followed within twenty-four hours by a severe reaction. The latter reaction persisted for about ten days and was controlled finally by the administration of sufficient ACTH and corticoids. After the subsidence of the reaction, it was decided to dilute the extract further and to give the patient minute amounts. Accordingly, he was given 0.01 ml. of a 1:1 million dilution intracutaneously weekly for four doses. No apparent reaction followed the first three injections, but after the fourth dose he developed such a severe generalized eruption that he had to be hospitalized for some time before the dermatitis was controlled. The eruption gradually subsided until the skin was almost clear; in fact, according to the patient, following his recovery the skin seemed better than at any previous time since the onset of the eruption. The patient at present is receiving only symptomatic treatment.

This case report illustrates strikingly one of the problems of hyposensitization with the extracts of inhalant allergens, namely, the exquisite degree of sensitization which may be present in a small number of patients, making treatment so difficult that it may have to be discontinued, as was true in three of our five patients. In the patient just cited, it is difficult to explain why no reactions followed the first three injections of 0.01 ml. of the 1:1 million dilution but did occur after the fourth dose. Whether the first three injections had been given to him in a refractory period following his previous reaction and were tolerated for that reason is mere speculation and remains to be proved. This possibility is suggested, however, by the striking improvement which followed his recovery from the reaction. This may have its counterpart in the refractory period of sensitization noted in guinea pigs after recovery from mild anaphylactic shock and similar refractory states (anergy) and also seen in human patients after recovery from constitutional reactions produced at times by injections of pollen extracts.

It is to be noted in the other patients with exquisite reactions to extremely small dosage that such reactions were induced repeatedly by the same dosage. This was true in all cases except the one just cited. Whenever possible, after the subsidence of the reaction, the patient was given a similar dose of either buffered saline or of histamine (1:1 million) by the same route to see if the reaction could be induced nonspecifically, but in no instance did a reaction follow the injection of any agent other than that of the extract to which the patient was specifically allergic.

Fortunately, as already noted, the exquisite type of reaction described above is quite uncommon. It occurred especially in patients with generalized

eruptions, as for example in all five patients included in Table V. However, some of our patients who also had generalized eruptions were able to tolerate high dosage without difficulty. Nevertheless, in treating this type of patient one must be sure to start with extremely dilute extracts to avoid aggravating the already existing dermatitis.

Of interest also in this group of patients was the fact that in those patients who had both atopic dermatitis and hay fever and who developed a reaction after the injection of pollen extract, the ensuing skin reaction always was of the delayed, eczematous, or papular type rather than of the immediate urticarial wheal which at times follows hyposensitizing injections of pollen extracts in patients with hay fever.

The immediate type of reaction was seen in only one patient, a woman who had both atopic dermatitis and asthma, and in this patient the reaction was induced experimentally by the injection of 0.1 ml. ragweed pollen extract (0.01 N) intracutaneously. Marked sneezing followed immediately after the injection and persisted for two days. Upon the third day after injection, the patient developed a moderately severe eruption in the antecubital fossae, wrists, and neck, which cleared within a week after appropriate treatment. Later, when the eruption had practically disappeared, the patient was again injected intracutaneously with 0.1 ml. of a more concentrated ragweed extract (0.4 N). Within a short time she began to sneeze, cough, and wheeze. This was followed later by intense itching in those areas previously affected by the dermatitis, namely, the antecubital fossel, wrists, face, and neck. The respiratory symptoms disappeared within thirty minutes after an injection of epinephrine, but some hours later she had a severe exacerbation of the dermatitis affecting the previously involved skin of the antecubital fossae, wrists, and neck, as well as that of the face which, according to the patient, had been clear previously. The itching was extremely intense, lasted three days, and then gradually lessened until only mild itching remained. Slight wheezing persisted for two days. The patient did well with specific allergy treatment given the following year, after which the skin condition cleared up completely.

This case illustrated strikingly, as did others in whom reactions followed either the usual hyposensitizing injections or the deliberately induced ones, that even if an immediate, urticarial, or atopic type of reaction (such as sneezing or asthma) is first induced, the subsequent reaction affecting the skin in patients with atopic dermatitis is likely to be delayed in onset and to resemble that of the existing dermatitis. It is exceedingly important that the delayed character of these reactions be fully appreciated by the attending physician. If not, the patient will continue to be injected with increasing amounts of the allergenic extract, which in turn will bring about subsequent and continued aggravation of the dermatitis rather than its amelioration. Failure to realize this or to recognize it in treated patients can lead to aggravation of the dermatitis. This, as I learned from early personal experience, may cause patients to become discouraged and to discontinue treatment, as exemplified in the following case report.

V. S., a 2-year-old girl, was first seen in December, 1946, with recurrent atopic dermatitis affecting the cheeks, neck, and flexures. The dermatitis had been present since early infancy (2 to 3 weeks of age). The parents were told that the "patient would grow out of it." The child had been treated by local ointments, which on one occasion caused a marked flare-up on the face. The patient improved at the seashore but the condition returned shortly after her return home. Intracutaneous skin tests were positive to ragweed, house dust, wool,

milk, chocolate, orange, and tomato. The child improved considerably after the elimination of wool, tomato, orange, and milk but had a flare-up in August, 1947, while at the seashore, coincident with the onset of slight ragweed hay fever (for the first time). The condition became worse on her return home. Desensitization with autogenous house dust was begun, with questionable improvement at first. The patient grew increasingly worse, so that her parents decided to discontinue all treatment and move to the seashore, where she improved remarkably. In reviewing her history later, it was noticed (but not recognized at the time) that the patient seemed somewhat worse two to three days after injections and that the dermatitis improved just before she returned for her next treatment. The relationship between her worsening skin condition and the hyposensitizing injection was not recognized, however, because of the delayed onset and an unawareness of the possibility that the treatment was responsible for the aggravation.

It is my belief also that similar failure to recognize the delayed reaction by those who administer hyposensitizing injections (as house dust) to these patients probably explains the reported lack of success with this type of treatment in atopic dermatitis patients.

A question often raised in relation to hyposensitization treatment in patients with atopic dermatitis concerns the results of this therapy. We tried to obtain an answer to this question by reviewing the case records of the 101 patients whom we had followed for a long enough period to record the results. A summary of these data is contained in Table VI. Inspection of the latter shows that the results of treatment generally were good. Thus, the dermatitis cleared and subsequently did not recur in thirty-two patients. In an additional forty-two the result was considered as "good" when the skin condition improved to the extent that the patient had either only a mild eruption or occasional mild recurrences. In seventeen patients only slight reduction in the dermatitis (recorded as fair) was noted, and in six there either was no change at all or the skin condition became worse.

TABLE VI. RESULTS OF TREATMENT

CONDITION OF SKIN	PERIOD OF OBSERVATION				TOTAL
	0-6 MONTHS	6 MONTHS TO 1 YEAR	1-3 YEARS	OVER 3 YEARS	
Clear	0	5	14	13	32
Good	5	15	15	11	46
Fair	1	7	4	5	17
No change	2	2	2	0	6
Totals	8	29	35	29	101

The management of all our patients with atopic dermatitis, as described in my previous publications, consisted first of attempts at elimination of test-positive foods from the diet and the avoidance as much as possible of contact with the offending inhalant allergens (especially house dust and wool). Additional symptomatic measures were employed in all cases to relieve the itching and to prevent further damage caused by scratching the injured skin areas. Oral administration of drugs, consisting usually of antihistamines and only occasionally of corticoids, was utilized whenever required, along with local applications to the skin of bland, nonirritating medicaments. If these

measures failed to clear the dermatitis, after a lapse of several weeks or longer, in patients allergic to inhalant allergens that could not be avoided (for example, dust, pollens, and molds), hyposensitization treatment with extracts of those allergens was instituted. This was found necessary in ninety-five of the 101 patients treated. Of five patients in whom dermatitis cleared completely in from six months to one year, improvement followed exclusion of test-positive foods from the diet in two patients. Of five patients who improved within six months and whose results were considered good, one improved only after dietary exclusion and one after complete wool elimination. Of the fifteen with a good result within six months to one year, one improved on dietary exclusion alone. This also was true of one patient of the seven considered to have only a fair result.

If we exclude from consideration the six patients treated entirely by elimination and/or avoidance, there remain ninety-five patients in whom hyposensitization with extracts of inhalant allergens was utilized. Good or excellent results were obtained in all but twenty-two, and actual failures were seen in only six. Even of the six who failed to respond, there were possible reasons for failure in three patients; one patient refused to cooperate in carrying out proper dietary and inhalant avoidance, and the other two reported too irregularly for us to determine the effect of the treatment. Actually, therefore, few patients who cooperated in treatment failed to receive some measure of relief, and most patients did rather well.

Therefore, from the results obtained in our series of patients, it is my opinion that the treatment of patients with atopic dermatitis, most of whom received hyposensitizing injections of allergenic extracts, compares very favorably with and, in fact, might even be better than the same treatment of a similar group of asthmatic patients.

SUMMARY

Hyposensitization with extracts of inhalant allergens, including house dust, ragweed, and timothy pollens and such atmospheric molds as alternaria and hormodendrum, is associated at times with certain difficulties which are reviewed in the present report. Of 183 patients with atopic dermatitis, either alone or combined with other allergic manifestations, 125 received hyposensitizing injections of extracts of one or more of the above-mentioned allergens. Thirty-four patients had a total of forty-nine reactions, usually after the injection but also in a few patients after skin testing or deliberate experimental induction. The reaction usually was temporary and could be obviated by reducing the dose and later increasing it more gradually. In five patients, however, reactions consistently followed extremely minute dosage, with subsequent attempted increases resulting in aggravation of the dermatitis rather than its amelioration.

Reactions following injections are delayed in onset from twelve to twenty-four hours or longer. They may go unrecognized, which explains some of the

reported failures in hyposensitization treatment. Awareness of this possibility and exercise of adequate caution to prevent the onset of reactions will bring about better response to treatment.

Results of treatment were evaluated in 101 patients. Six patients were successfully treated by elimination of foods or inhalants alone, and ninety-five also received hyposensitization treatment. Excellent or good results were obtained in seventy-three and actual failures in only six. On the whole, the results obtained compare favorably with those obtained in patients with allergic asthma treated in similar fashion.

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LONG-TERM EVALUATION OF TRIAMCINOLONE THERAPY IN ALLERGIC DISEASES

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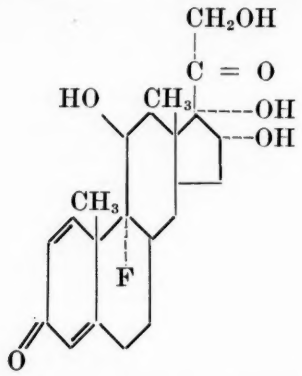
IN MARCH, 1957, one of us reported on the use of a new synthetic corticosteroid,[1] triamcinolone,* in seventeen allergic patients treated for only sixteen weeks. This report is a continuation of that study. Since our previous report, two hundred patients have been treated with triamcinolone for two to sixty-eight weeks.

Triamcinolone (9-alpha-fluoro-16-alpha-hydroxyprednisolone) was synthesized by Bernstein and his co-workers.[2] The structural formula is given below:



Untoward pharmacologic effects are few. The effects of triamcinolone on sodium and potassium excretion and calcium, phosphorus, and nitrogen metabolism have been determined in several human metabolic studies.[3-7] The results of these studies showed practically no sodium retention or potassium loss, even when triamcinolone was used in moderately large doses (12 to 24 mg. per day). It was found that many of the patients showed a sodium diuresis. With usual therapeutic doses, adequate to control symptoms, the influence on calcium, phosphorus, and nitrogen metabolism was negligible.

METHODS

Two hundred patients with various allergic diseases were treated with triamcinolone for two to sixty-eight weeks. Forty-five of these had been treated

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*Aristocort, supplied for this study by Lederle Laboratories Division of American Cyanamid Company, Pearl River, New York.

with prednisone or prednisolone, with good control of symptoms, for four to 156 weeks. They were then given triamcinolone in a dose sufficient to produce the same control of symptoms. This was done to compare the anti-inflammatory and side effects of these corticosteroids. Of the 200 patients studied, ninety had asthma, seventy-seven had allergic rhinitis (forty-six perennial, thirty-one hay fever), twelve had atopic dermatitis, two had poison ivy dermatitis, eleven had contact dermatitis, three had acute urticaria and five had chronic urticaria. Their ages ranged from two to seventy-five years. Duration of therapy was two to sixty-eight weeks. Diets were not restricted as to sodium intake, nor was any supplemental potassium given. All patients underwent complete physical examination at their first visit. They were seen weekly at which time blood pressure, pulse, vital capacity, weight, and physical examination were recorded. All patients were receiving desensitization therapy. Other symptomatic therapy was given as indicated (sympathomimetics, antibiotics, and antihistamines). These patients were from the clinic of The Institute of Allergy of The Roosevelt Hospital as well as from our private practice.

Table I summarizes the comparative study of forty-five allergic patients treated for four to 156 weeks with prednisone or prednisolone and then given triamcinolone in an amount sufficient to produce the same control of symptoms. The patients have been treated from four to sixty-eight weeks.

On a weight basis, triamcinolone was found to have approximately twice the anti-inflammatory potency of prednisone and prednisolone. The blood pressure dropped in seventeen patients (10 to 15 mm. Hg) and remained stationary in twenty-eight. The weight decreased slightly in fifteen patients (2 to 8 pounds), one increased slightly (2 pounds), and thirty-nine remained the same. On prednisone and prednisolone, twenty-five patients had various side effects as compared with only twelve patients who were on triamcinolone. Of these twenty-five patients with side effects on prednisone or prednisolone, fifteen showed none when given triamcinolone, five retained the same side effects, five lost the original side effects but developed others, and side effects developed in two who had had none on prednisone or prednisolone. Five patients had ecchymosis while taking triamcinolone, and in none was there any alteration in the blood to explain this reaction. One patient had had an active duodenal ulcer for two years while taking prednisone. When she was changed to triamcinolone, x-ray examination disclosed that the ulcer was healed at the end of six months, and she was asymptomatic. The diet, antispasmodics, and antacids were continued as before triamcinolone therapy. One asthmatic patient (a man) developed active tuberculosis while on prednisone therapy. The asthma could not be controlled with conventional therapy alone. Isoniazed and para-aminosalicylic acid were given, without discontinuance of the corticosteroid, for sixty-eight weeks. At the end of this time, the pulmonary x-ray findings showed no activity of tuberculosis, the sputum was negative for tubercle bacilli, and the patient's general health was good.

Table II shows the results of treating ninety asthmatic patients for three to sixty-eight weeks with triamcinolone. The maintenance doses varied; eight patients were maintained with 2 mg. per day, six with 3 mg., twenty-nine with

TABLE I. COMPARISON OF PREDNISONE OR PREDNISOLONE WITH TRIAMCINOLONE

NO.	DIAGNOSIS	NO. OF WEEKS TREATED		MG. PER 24 HOURS		BLOOD PRESSURE	WEIGHT CHANGE	CLINICAL RESPONSE	SIDE EFFECTS	
		PREDNISONE OR PREDNISOLONE	TRIAMCINOLONE	PREDNISONE OR PREDNISOLONE	TRIAMCINOLONE	TRIAMCINOLONE	TRIAMCINOLONE	TRIAMCINOLONE	PREDNISONE OR PREDNISOLONE	TRIAMCINOLONE
1	Asthma	26	68	10	6	No change	No change	No change	None	None
2	Asthma	4	68	15	8	No change	No change	Better	None	None
3	Asthma	104	68	30	12	Decreased	Decreased	Better	None	None
4	Asthma	114	26	10	4	Decreased	No change	No change	Edema, increased blood pressure	None
5	Asthma	26	68	10	6	Decreased	Decreased	No change	None	Hirsutism
6	Asthma	26	68	15	6	Decreased	Increased	No change	None	Increased appetite
7	Asthma	82	60	15	8	Decreased	No change	No change	Increased blood pressure, edema	None
8	Asthma	13	66	15	6-8	Decreased	Decreased	No change	None	None
9	Asthma	34	67	10	5	No change	No change	No change	None	None
10	Asthma	12	31	10	6	No change	No change	No change	None	None
11	Eczema	17	33	10	5	Decreased	Decreased	Better	Indigestion	Ecchymosis, no indigestion
12	Asthma	14	8	10	6	Decreased	Decreased	No change	None	None
13	Perennial rhinitis	16	29	5	2	No change	No change	No change	None	None
14	Asthma	10	67	10	6	No change	No change	No change	Indigestion, acne, abdominal pain	Indigestion, abdominal pain
15	Asthma	50	67	20	8	Decreased	Decreased	No change	Moon facies	Moon facies
16	Asthma	104	67	25	12	Decreased	Decreased	No change	Hirsutism, moon facies	Hirsutism, moon facies
17	Asthma	8	6	10	4	No change	No change	No change	None	None
18	Asthma	104	42	30	12	No change	No change	No change	Moon facies	Moon facies, ecchymosis
19	Eczema	12	17	20	8	Decreased	Decreased	Better	Moon facies	None
20	Asthma	104	58	25	12	No change	No change	No change	Moon facies edema	Purpura
21	Asthma	6	38	15	6	No change	No change	No change	Abdominal pain	None
22	Asthma	4	13	10	6	No change	No change	No change	None	None
23	Asthma	156	42	10	6	No change	No change	No change	Acne, peptic ulcer, hirsutism	Hirsutism, ulcer healed

24	Asthma	104	26	30	16	Decreased	Decreased	No change	Nausea, moon facies, hirsutism, edema	Indigestion, ecchymosis, moon facies
25	Asthma	52	52	20	12	Decreased	Decreased	No change	Nausea, bloating	None
26	Asthma	7	39	15	8	No change	No change	No change	None	None
27	Perennial rhinitis	52	20	5	2	No change	No change	No change	None	None
28	Asthma	8	52	30	16	No change	Decreased	No change	Edema, bloating, indigestion	None
29	Asthma	19	52	10	6	No change	Decreased	No change	Indigestion, bloating	None
30	Asthma	8	40	10	5	No change	No change	No change	None	None
31	Asthma	8	52	20	10	Decreased	Decreased	No change	Indigestion, edema, increased blood pressure	None
32	Perennial rhinitis	56	52	5	3	No change	Decreased	No change	Edema	Ecchymosis, no edema
33	Asthma	44	32	10	4	No change	No change	No change	Indigestion	None
34	Asthma	35	32	10	8	No change	No change	No change	None	None
35	Asthma	16	39	10	6	No change	No change	No change	None	None
36	Perennial rhinitis	10	18	10	6	No change	No change	No change	None	None
37	Asthma	26	26	30	12	Decreased	Decreased	Better	Increased blood pressure, edema	None
38	Asthma	32	23	15	6	No change	No change	Better	Nausea, bloating, pyrosis	None
39	Asthma	82	16	20	10	Decreased	No change	No change	Headache	None
40	Asthma	22	28	10	4	No change	No change	No change	None	None
41	Asthma	96	18	10	6	No change	No change	No change	Indigestion	None
42	Asthma	96	12	20	8	Decreased	No change	No change	Increased blood pressure	Ecchymosis
43	Perennial rhinitis	4	4	10	6	No change	No change	No change	None	None
44	Asthma	58	6	20	8	No change	No change	No change	Moon facies, increased blood pressure	None
45	Eczema	34	10	15	6	No change	No change	No change	Moon facies, increased blood pressure	None

4 mg., eight with 5 mg., twenty-two with 6 mg., nine with 8 mg., six with 12 mg., and two with 16 mg. The patients who required 8 mg. or more per day as a maintenance dose had many complications, such as severe emphysema, pulmonary fibrosis, and chronic bronchitis. All had had their disease for many years. With steroids, all the patients can now carry on their usual daily duties. There were forty-eight separate side effects in twenty patients. One patient developed severe osteoporosis with three spontaneously fractured vertebrae. All other patients who complained of backaches were x-rayed (four patients), but none showed x-ray evidence of osteoporosis. All nineteen patients with gastrointestinal complaints were x-rayed and showed no gastrointestinal ulceration. In all cases the symptoms were easily controlled with antacids, antispasmodics, or both. In none has the drug had to be discontinued because of severity of side effects. The patient with spontaneous fractures of the spine had to be maintained on steroids because the symptoms of asthma could not be controlled without them. Two patients became pregnant during treatment.

TABLE II. PATIENTS WITH ASTHMA

Ages	3-70 years
Duration treatment	3-68 weeks
Maintenance dose per 24 hr.	2-16 mg.
No. of patients	90
Mental depression	1
Osteoporosis	1
Spontaneous fractures of vertebrae	1
Nervousness	1
Hirsutism	7
Moon facies	6
Acne	3
Ecchymosis	6
Hyperhidrosis	2
Enuresis	1
Leg cramps	4
Gastrointestinal complaints:	
Indigestion	4
Bloating	4
Epigastric distress	5
Nausea	1
Abdominal pain	5

They were treated with 6 to 10 mg. per day throughout their pregnancies, which were normal. Delivery of one was normal, and one had a cesarean section, which had no relationship to triamcinolone. A cord blood sample of the baby showed normal 11-17 hydroxysteroids.

ALLERGIC DERMATOSES

The group with allergic dermatoses consisted of thirty-three patients, twelve with atopic dermatitis, two with poison ivy, three with acute urticaria, five with chronic urticaria, and all with contact dermatitis.

The results obtained by treatment of these patients with triamcinolone are summarized in Table III.

Control of symptoms was achieved in two to three days. Maintenance treatment given in a single daily dose gave results as good as when the doses

were divided. In one instance enuresis ceased when the dose was diminished to less than 4 mg. per day. In another instance, hyperhidrosis ceased when the dose was decreased to below 6 mg. per day.

TABLE III

DIAGNOSIS	NUMBER OF PATIENTS	DURATION OF TREATMENT (WEEKS)	DOSE RANGE PER 24 HOURS (MG.)	MAINTENANCE DOSE PER 24 HOURS (MG.)	CLINICAL RESPONSE	SIDE EFFECTS
Eczema	12	7-40	1-12	4	Good	0
Poison ivy	2	3-10	1-12	2	Good	Enuresis
Acute urticaria	3	3-6	1-12	3	Good	Tiredness
Chronic urticaria	5	3-34	1-16	4	Good	Hyperhidrosis
Contact dermatitis	11	2-3	2-12	3	Good	0

ALLERGIC RHINITIS

Seventy-seven patients were treated for allergic rhinitis; thirty-one had seasonal symptoms and forty-six perennial. Table IV summarizes the treatment of these patients with triamcinolone.

TABLE IV

DIAGNOSIS	NUMBER OF PATIENTS	AGES	DURATION OF TREATMENT (WEEKS)	DOSE RANGE PER 24 HOURS (MG.)	MAINTENANCE DOSE PER 24 HOURS (MG.)	CLINICAL RESULTS	SIDE EFFECTS
Seasonal rhinitis	31	7-47	2-20	1-12	4-6	Good	Two patients had indigestion
Perennial rhinitis	46	16-75	2-52	1-12	4	Good	1—Acne 1—Mental depression

RHINITIS

An interesting observation was that control of seasonal rhinitis with triamcinolone alone was very difficult unless fairly large doses (8 to 16 mg.) were used, whereas, if long-acting antihistamines were used concomitantly very little added steroid was necessary to get complete symtomatic control. In one instance of mental depression, it was necessary to reduce the dose of triamcinolone to 3 mg. per day before the depression disappeared.

Table V summarizes the side effects in the 200 patients treated for two to sixty-eight weeks. Thirty patients showed sixty-four side effects, nine had more than one side effect, and the remainder had a single side effect. The mental depression occurring in three patients disappeared in all cases upon lowering of the dose. In all patients the ecchymosis could be stopped by reducing the dose but not below the level necessary for good control of symptoms. Blood counts, bleeding, clotting time, prothrombin time, and platelets were all within normal limits. One patient had spontaneously fractured vertebrae due to

TABLE V. SUMMARY OF SI EFFI

PATIENT	DIAGNOSIS	DURATION OF TREATMENT (WEEKS)	AVERAGE DOSE (MG.) PER 24 HOURS	MENTAL DEPRESSION	NERVOUSNESS	HIRSUTISM	MOON FACIES	ECCHYMOSIS	HYI DR
1	Asthma	42	8						
2	Atopic dermatitis	68	2-6						
3	Contact dermatitis	6	4-8						
4	Asthma	68	8			x	x	x	
5	Asthma	36	6						
6	Asthma	8	4	x					
7	Perennial rhinitis, urticaria	16	6						
8	Asthma	52	16			x	x	x	
9	Asthma	68	12			x	x		
10	Asthma	68	4					x	
11	Perennial rhinitis	24	6	x					
12	Urticaria	16	8						
13	Asthma	8	6		x				
14	Urticaria	28	6-8						
15	Asthma	30	8					x	
16	Perennial rhinitis	24	6	x					
17	Asthma	68	6			x			
18	Asthma	68	6						
19	Asthma	68	4						
20	Asthma	60	6					x	
21	Asthma	52	8						
22	Asthma	68	4-6			x	x		
23	Asthma	68	4-8			x	x		
24	Asthma	68	4-6						x
25	Asthma	20	6-8						
26	Asthma	18	4-6						
27	Asthma	68	4-8			x	x	x	
28	Asthma	42	4-6						
29	Hay fever	10	8-10						
30	Hay fever	12	6-8						

severe osteoporosis, but because of the severity of her asthma steroids could not be eliminated. The symptoms of the spinal fractures were completely controlled by estrogen and androgen therapy. (Conjugated equine estrogens, 5 mg. twice a day, and methyltestosterone, 5 mg. sublingually twice a day, for five weeks and then one week of rest, etc.)

SUMMARY

Two hundred patients with various allergic diseases were treated with triamcinolone for two to sixty-eight weeks in dosage of 2 to 16 mg. per day. There was good control of symptoms in all patients. By transferring forty-five

Y OF SIDE EFFECTS OF 200 PATIENTS

ECCHYMOSIS	HYPERHIDROSIS	ENURESIS	LEG CRAMPS	GASTROINTESTINAL COMPLAINTS	ACNE	TIREDNESS	HEADACHE	OSTEOPOROSIS	FRACTURED VERTEBRAE
				Indigestion, epigastric distress, bloating					
					x				
		x							
x					x	x			
			x						
							x		
x				Nausea and abdominal pain	x				
								x	x
x									
					x				
	x			Indigestion, epigastric distress, abdominal pain					
	x								
x									
				Abdominal pain					
			x						
			x						
				Indigestion, bloating, epigastric distress					
x									
			x						
				Indigestion, abdominal pain					
				Indigestion, epigastric distress, bloating					
	x								
				Bloating and nausea					
		x							
x				Abdominal pain					
				Indigestion					
				Epigastric distress and indigestion					
				Indigestion					

patients from prednisone and prednisolone, it was found that, milligram for milligram, the potency of triamcinolone was twice that of prednisone and prednisolone and that side effects occurred in only twelve patients, as compared to twenty-five on prednisone and prednisolone. Fifteen per cent of these two hundred patients developed sixty-four side effects, only one severe enough to discontinue treatment. This patient did develop spontaneous fractures of three vertebrae and, because of the severity of symptoms, the steroid had to be maintained. One patient had an active duodenal ulcer which healed in response to triamcinolone therapy. In one case active tuberculosis continued to heal while the patient was on triamcinolone and antituberculous therapy. Two patients,

were maintained on triamcinolone throughout pregnancy; one of them had a cesarean section performed without any complications. Cord blood taken at birth showed normal 11-17 hydroxysteroid levels.

CONCLUSIONS

Triamcinolone is a new potent synthetic corticosteroid. From this study of two hundred patients, we can conclude that its potency in allergic diseases is approximately twice that of prednisone or prednisolone.

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PEPTIC ULCER AMONG ALLERGIC PATIENTS ON LONG-TERM TRIAMCINOLONE* THERAPY

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WITH the increased use of adrenal corticosteroids during the past few years, there have appeared many reports of their undesirable side effects. One of the most serious has been peptic ulceration, with or without perforation or hemorrhage.[1, 2, 4-7] This has been a deterring factor in the use of these agents, especially in patients with a previous history of peptic ulcer.

There have been few published reports[2, 3] of routine serial x-rays of the upper gastrointestinal tract of patients who were being maintained on long-term corticosteroid therapy.

It is the purpose of this study to determine the incidence of peptic ulceration in a group of allergic patients maintained on triamcinolone for a long period of time.

MATERIALS AND METHODS

Twenty-four patients were selected for this study. Of these, twenty had asthma, one had chronic urticaria, one had eczema, one had perennial rhinitis with rheumatoid arthritis, and one had uncomplicated perennial rhinitis. All patients had had allergic management for many months to years, without adequate control of symptoms, prior to triamcinolone therapy. Six patients had had other corticosteroid therapy prior to this study. Only one patient had an active duodenal ulcer at the time the first x-ray was taken at the beginning of this study. The patients were from The Institute of Allergy of the Roosevelt Hospital in New York City and from our private practice. All patients had received triamcinolone for twelve to twenty-six weeks with no gastrointestinal symptoms prior to the start of this study. Upper gastrointestinal x-ray examinations were performed every three to four months until four had been completed. These studies were performed in the usual manner, with barium sulfate as the single contrast medium. All patients were fluoroscoped, and spot films were taken when indicated.

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*Aristocort, supplied by Lederle Laboratories Division of American Cyanamid Co., Pearl River, New York.

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TABLE

DISEASE	AGE	SEX	DURATION OF DISEASE (YEARS)	DURATION OF TREATMENT WITH TRIAMCINOLONE (WEEKS)	DOSE OF TRIAMCINOLONE PER 24 HOURS (MG.)	GASTROINTESTINAL	
						1	2
Asthma, chronic bronchitis	46	F	32	104	8-16	7/25/57	11/29/57
Asthma, cor pulmonale, kyphoscoliosis	51	F	45	105	12-16	7/29/57	12/21/57
Chronic obstructive pulmonary emphysema, asthma	60	M	10	102	4-12	8/ 1/57	3/31/58
Chronic obstructive pulmonary emphysema, asthma	43	F	8	106	4-8	8/ 6/57	3/ 4/58
Asthma, pulmonary emphysema	51	M	42	104	8-12	7/30/57	12/ 7/57
Bullous emphysema, asthma	67	F	19	93	6-12	7/30/57	12/ 6/57
Asthma, perennial rhinitis	34	M	23	84	4-12	8/10/57	12/21/57
Chronic urticaria, chronic sinusitis, perennial rhinitis	38	M	3½	78	2-10	8/ 6/57	12/17/57
Asthma, chronic pulmonary emphysema	58	F	9	100	6-10	8/ 6/57	1/22/58
Asthma, chronic pulmonary emphysema	65	M	17	82	4-10	8/10/57	12/28/57
Asthma, chronic pulmonary emphysema	34	F	24	104	6-12	7/31/57	11/15/57
Asthma, perennial rhinitis	48	M	10	94	4-8	8/ 2/57	12/30/57
Asthma, perennial rhinitis	48	F	5	96	4-8	7/31/57	11/22/57
Asthma, hay fever	40	F	22	84	4-12	9/ 6/57	12/10/57
Eczema, perennial rhinitis	25	F	25	104	4-6	9/13/57	1/15/58
Asthma, pulmonary emphysema	32	F	17	86	8-12	10/ 6/57	3/ 1/58
Perennial rhinitis, rheumatoid arthritis	47	M	2	68	4-16	11/26/57	2/20/58
Chronic obstructive pulmonary emphysema, asthma, cor pulmonale	63	M	18	68	4-8	6/28/57	10/14/57
Asthma, chronic sinusitis	40	F	12	108	8-16	4/15/57	8/15/57
Perennial rhinitis	77	F	12	96	2-6	8/23/57	1/ 3/58
Asthma	23	F	12	102	4-12	7/14/57	11/ 5/57
Asthma, pulmonary emphysema	47	F	16	110	4-12	8/13/57	1/24/58
Asthma	64	M	32	114	8-12	10/12/57	3/14/58
Asthma	46	M	24	110	8-16	7/15/57	12/15/57

TABLE I

X-RAY SERIES (DATE)		RESULTS OF GASTROINTESTINAL SERIES				SIDE EFFECTS
3	4	1	2	3	4	
6/27/58	10/31/58	Neg.	Neg.	Neg.	Neg.	Moon facies
6/13/58	10/31/58	Neg.	Neg.	Neg.	Neg.	Hirsutism, osteoporosis, spontaneous fractures (D_{10}, L_{1+4}), potassium loss
6/20/58	11/18/58	Neg.	Neg.	Neg.	Neg.	None
6/26/58	1/21/59	Neg.	Neg.	Neg.	Neg.	None
7/12/58	1/17/59	Neg.	Neg.	Neg.	Neg.	None
7/25/58	11/15/58	Neg.	Neg.	Neg.	Neg.	Osteoporosis, spontaneous fractures (L_{1+3})
6/21/58	12/ 6/58	Neg.	Neg.	Neg.	Neg.	None
6/ 3/58	1/23/59	Neg.	Neg.	Neg.	Neg.	Excess perspiration, above 6 mg. daily
6/24/58	11/ 4/58	Neg.	Neg.	Neg.	Neg.	None
7/23/58	1/31/59	Neg.	Neg.	Neg.	Neg.	None
4/13/58	10/29/58	Neg.	Neg.	Neg.	Neg.	Some moon facies
6/28/58	12/ 2/58	Neg.	Neg.	Neg.	Neg.	None
6/25/58	12/ 3/58	Neg.	Neg.	Neg.	Neg.	None
6/19/58	11/ 8/58	Duodenal ulcer, 4 yr. duration	Healed	Healed	Healed	Hirsutism mild, no GI complaints
5/20/58	12/15/58	Neg.	Neg.	Neg.	Neg.	None
7/26/58	12/20/58	Neg.	Neg.	Neg.	Neg.	Moon facies
6/14/58	11/29/58	Neg.	Neg.	Neg.	Neg.	None
3/15/58	7/14/58	Neg.	Neg.	Neg.	Neg.	None
2/ 8/58	7/15/58	Neg.	Neg.	Neg.	Neg.	Hirsutism
6/15/58	11/24/58	Neg.	Neg.	Neg.	Neg.	None
4/13/58	9/21/58	Neg.	Neg.	Neg.	Neg.	Moon facies
6/24/58	1/14/59	Neg.	Neg.	Neg.	Neg.	Pains in chest
7/23/58	2/ 4/59	Neg.	Neg.	Neg.	Neg.	None
6/14/58	1/16/59	Neg.	Neg.	Neg.	Neg.	Moon facies

RESULTS OF STUDY

One patient had had an active duodenal ulcer, proved by x-ray, four years prior to institution of triamcinolone therapy. This patient had been receiving prednisone, 10 to 15 mg. daily, during this period, supplemented by aluminum hydroxide, antispasmodics, and a convalescent ulcer diet. The first x-ray taken before triamcinolone was started showed an ulcer crater in the duodenum. Three months later, after the patient had received triamcinolone in doses of 4 to 12 mg. daily (usual dose, 4 to 6 mg.), there was no x-ray evidence of ulcer. For the duration of the study, the ulcer remained healed as demonstrated by x-ray study, and rare gastrointestinal symptoms occurred in spite of continued triamcinolone therapy.

The remaining twenty-three patients had no gastrointestinal complaints and no x-ray evidence of peptic ulceration. The dose of triamcinolone ranged from 2 to 16 mg. daily, given in divided doses. Treatment lasted from sixty-eight to 114 weeks (including the 12 to 26 weeks prior to the first x-ray). The x-ray examinations were performed over a period of twelve to eighteen months. Twelve of the patients had various side effects not related to the gastrointestinal tract; the remaining twelve had none.

SUMMARY AND CONCLUSIONS

Twenty-four patients with various allergic diseases were treated daily with triamcinolone for sixty-eight to 114 weeks. The upper gastrointestinal tract was x-rayed four times over a period of fifty-two to seventy-eight weeks, with no evidence of peptic ulcer except in one patient who had had a duodenal ulcer at the time of the first x-ray but on each of the three succeeding examinations showed a healed ulcer. Granted that twenty-four patients is a small number upon which to draw any conclusions, it would appear, by comparison with other corticosteroids,[1-3] that triamcinolone may not be as ulcerogenic as previously used steroids.

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A SURVEY OF THE HAY FEVER PLANTS AND IMPORTANT ATMOSPHERIC ALLERGENS IN THE PHOENIX, ARIZONA, METROPOLITAN AREA

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INTRODUCTION

THE first extensive publication concerning pollinosis in Arizona was that by Watson and Kibler[1] in which an attempt was made to list all the plants thought to be capable of causing hay fever in the Southwest. Anemophilous plants were then classified as to their importance on the basis of field and clinical observations. Following this, E. W. Phillips, a local physician, became the leading investigator of the pollen allergens in the Phoenix metropolitan area. He tested his patients intradermally with pollen extracts made from naturally ripened pollen collected in the Phoenix area. By correlating his clinical records with concise field observations of pollinating plants, he assembled data for numerous publications[2-10] concerning the treatment of pollinosis and the seasonal occurrence of specific pollen allergens.

In 1944 Randolph and McNeil[11] published the first and only atmospheric study that has been made of pollen grains in the Phoenix area over an extended period of time. Their investigations were made from 1934 through 1936. Due to the standardization of the technique for atmospheric pollen testing in 1946 by the Pollen Survey Committee of the Research Council of the American Academy of Allergy,[12-13] the concentrations of atmospheric pollen grains found in the Randolph and McNeil study cannot be compared with observations presented in this article. In reporting their investigation, Randolph and McNeil state: "The slides are mounted at a 45 degree angle on weather vane arrangement, protecting them from rain but allowing full exposure to the air. Because the slide automatically faces into the air currents, there is greater volume of pollen deposited on windy days than would be with the slide lying flat on the window ledge." Their data, however, can be used in a comparison of the general seasonal pollen occurrence.

The purpose of this article is twofold. First of all, it is my intention to present a survey of the plants considered to be responsible for inhalant allergies in the Phoenix, Arizona, metropolitan area. The second objective is to supply data and information concerning the kind, concentration, and seasonal

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occurrence of the atmospheric pollen grains and fungous spores found during a one-year investigation conducted from June 1, 1957, through May 31, 1958, in Phoenix and Tempe, Arizona. Presentations of this nature are common, for nearly every heavily populated community in the United States has information concerning its atmospheric allergens. The Phoenix area, however, has not had the advantage of a complete aerobiologic survey of allergenic pollen grains and fungous spores. Considering that this region is the population center of Arizona, the need and importance of atmospheric allergen data become evident.

MATERIALS AND METHODS

A botanical survey was conducted at the outset of this study to ascertain which plants, capable of causing pollinosis, could be found in the Phoenix area. All the anemophilous plants were considered along with a few entomophilous plants known to produce pollen in such quantities that many grains become air-borne. Concurrently, pollen samples were collected from the different plant species, and permanent microscope slides were prepared by mounting the pollen grains in glycerin jelly stained with basic fuchsin. Many different fungous spores were similarly prepared. Photomicrographs and camera lucida drawings were made of these pollen grains and fungous spores at a magnification of 970× obtained with a monocular Bausch & Lomb microscope.

The next step in this investigation was the selection of two collecting stations for purposes of exposing prepared slides to the atmosphere. One of the sites chosen for a station was located in the Goodwin Stadium on the campus of Arizona State University in Tempe, Arizona. The standard Durham gravity sampling device was placed on top of the press box at a point free from all obstructions, approximately 50 feet above the ground level. The second station was located on the administration building at Phoenix Union High School in downtown Phoenix. The sampling device was placed at a point about 40 feet from ground level on the edge of the roof. It was relatively free from obstruction except for a slightly higher section of the roof about 30 feet northeast of the sampler.

The atmospheric survey of the pollen grains and fungous spores at the two stations previously designated was obtained by the gravity method described by Durham[14] and approved by the American Academy of Allergy.[12-13] Slides coated with a thin layer of glycerin jelly stained with basic fuchsin dye were placed, face up, on the horizontal platform in the standard air-sampling device. Slides were exposed for forty-eight hours from 8 A.M. Monday to 8 A.M. Wednesday, from 8 A.M. Wednesday to 8 A.M. Friday, and for a seventy-two-hour period from 8 A.M. Friday to 8 A.M. Monday. All readings from these slides were converted to represent twenty-four-hour averages.

The slides were prepared for microscopic examination by placing a 4.84 sq. cm. cover slip on the glycerin jelly that had been softened by heat. The slides were then examined under oil immersion with a monocular microscope,

and identification was made by comparing the pollen grains and spores with the permanent mounts, photomicrographs, and camera lucida drawings. The counts were recorded under low-power magnification, using a 10× objective and 15× ocular. With this magnification, the entire area under the cover slip can be counted in twelve horizontal sweeps. Every other sweep was counted, however, for a total of six horizontal sweeps or an area of 2.42 sq. cm. Each total count was then divided by 2.42, which gave the average number of pollen grains or fungous spores per square centimeter. Finally, an interpolation was made, converting the number of pollen grains per square centimeter to the number

TABLE I. CONVERSION FACTORS

NAME OF LOCAL POLLEN (SCIENTIFIC AND COMMON)	NAME OF EXPERIMENTAL POLLEN* (SCIENTIFIC AND COMMON)	AVERAGE DIAMETER OF LOCAL POLLEN (MICRONS)	AVERAGE DIAMETER OF EXPERIMENTAL POLLEN (MICRONS)	CONVERSION FACTORS	
				LOCAL POLLEN	EXPERIMENTAL POLLEN
Cynodon dactylon (Bermuda grass)	*(Capriola) Cynodon dactylon* (Bermuda grass)	30.0	28.5	1.55	1.71
Sorghum halepense (Johnson grass)	*(Capriola) Cynodon dactylon* (Bermuda grass)	38.0	28.5	0.97	1.71
Amaranthus palmeri (careless weed)	*Amaranthus palmeri* (careless weed)	28.0	25.8	1.48	1.71
Atriplex species (saltbush)	*Salsola kali (pestifer)* (Russian thistle)	22.0	23.6	1.98	1.71
Beta vulgaris (sugar beet)	*Salsola kali (pestifer)* (Russian thistle)	22.0	23.6	1.98	1.71
Chenopodium species and miscellaneous chenopods	*Salsola kali (pestifer)* (Russian thistle)	24.0	23.6	1.65	1.71
Salsola kali (Russian thistle)	*Salsola kali (pestifer)* (Russian thistle)	26.0	23.6	1.41	1.71
Sarcobatus vermiculatus (greasewood)	*Salsola kali (pestifer)* (Russian thistle)	24.0	23.6	1.65	1.71
Dicoria canescens (dicoria)	*Franseria acanthicarpa* (Bur-ragweed)	22.0	22.0	3.16	3.16
Franseria species (false ragweed)	*Franseria acanthicarpa* (Bur-ragweed)	22.0	22.0	3.16	3.16
Hymenoclea species (burrobrush)	*Ambrosia elatior* (short ragweed)	20.0	20.0	3.60	3.60
Plantago species (plantain)	*Plantago lanceolata* (English plantain)	26.0	27.5	2.38	2.13
Rumex species (curly dock and canaigre)	*Rumex acetosella* (red sorrel)	30.0	21.5	1.75	3.40
Cupressus and *Juniperus* (cypress and juniper)	*Juniperus sabinoides* (mountain cedar)	27.0	22.8	1.96	2.75
Fraxinus velutina (Arizona ash)	*Fraxinus americana* (ash)	23.0	27.1	2.90	2.09
Olea europaea (olive)	*Fraxinus americana* (ash)	21.0	27.1	3.48	2.09
Populus fremontii (cottonwood)	*Populus virginiana* (cottonwood)	30.0	30.0	2.09	2.09
Morus species (mulberry)	*Ulmus americana* (elm)	20.0	31.2	3.70	1.56
Ulmus species (elm)	*Ulmus americana* (elm)	31.0	31.2	1.58	1.56

*Experimental pollen used by Durham.[14]

of grains per cubic yard of air. This was attained by using the standard conversion factors suggested by Durham,[14] who derived his data from experimental rates of fall for pollen grains as compared with pollen grains of *Ambrosia*

elatior L., the short ragweed. This conversion uses the factor 3.6 for short ragweed as a pivot for establishing conversion factors for other types of pollen. The rate of fall of a given pollen grain is divided into 3.6, and then the calculated factor is multiplied by the number of grains per centimeter on a slide. The product of this represents the number of pollen grains per cubic yard of air. Due to the difference in size of the local pollen grains as compared to the similar experimental pollen grains used by Durham, many of the experimental conversion factors had to be adjusted to local factors. This was accomplished by using the following formula as recommended by Durham[14]:

$$\text{Conversion factor for local pollen grain} = \frac{(\text{Diameter of experimental grain})^2 \left(\text{Conversion factor of experimental grain}\right)}{(\text{Diameter of similar local grain})^2}$$

In comparing "similar" pollen grains it was necessary, in many cases, to relate the size of grains from plants of the same family, rather than from the same genus, because the number of different local species being reported was greater than the number of experimental species previously determined. In calculating the conversion factor of pollen of the *Morus* species, however, a factor of a closely similar experimental pollen was not available; therefore, the comparison was made with pollen of *Ulmus* species, another plant of the order Utricales.

Table I gives the experimental conversion factors as established by Durham[14] and the calculated local factors.

Conversion factors could not be established for some pollen grains or for all the fungous spores. These counts were reported as number per square centimeter on a slide.

A final step in this investigation was the compilation of climatologic data for the Phoenix area and its comparison with the concentrations of atmospheric allergens.

RESULTS

Botanical Survey.—The following is a list of the important plants found in the metropolitan Phoenix area capable of causing pollinosis and the months in which they pollinate. All common names were taken from the list prepared by the Herbarium Committee of the American Academy of Allergy with the exception of the names indicated by asterisks, which were taken from *Arizona Flora* by Kearney and Peebles.[15]

Scientific Name	*Common Name*	*Time of Pollination (Inclusive)*	*Prevalence†*
AMARANTHACEAE			
Amaranthus palmeri	Careless weed*	May-November	++
CHENOPODIACEAE			
Allenrolfea occidentalis	Pickleweed*	August-November	–
Atriplex canescens	Wingscale saltbush*	July-October	–
Atriplex elegans	Wheelscale saltbush*	April-July	+
Atriplex lentiformis	Lens-scale saltbush	July-October	+
Atriplex polycarpa	Allscale saltbush	July-October	–
Atriplex wrightii	Annual saltbush	June-October	+

Bassia hyssopifolia	Smotherweed*	August-October	+
Beta vulgaris	Sugar beet	April-June	+
Chenopodium album	Lamb's-quarter	March, April	–
Chenopodium ambrosioides	Wormseed goosefoot*	July-September	–
Chenopodium murale	Nettle-leaf goosefoot	December-April	+
Chenopodium pratericola	Goosefoot*	March, April	–
Salsola kali	Russian thistle	May-November	++
Sarcobatus vermiculatus	Greasewood*	July-September	–
Suaeda torreyana	Seepweed*	July, August	+
COMPOSITAE			
Dicoria canescens	Dicoria	August-October	–
Franseria ambrosioides	Canyon ragweed	March, April	+
Franseria confertiflora	Slender ragweed	June-October	+
Franseria deltoidea	Rabbit bush	February-May	++
Franseria dumosa	Desert ragweed	March-May, October, November	–
Hymenoclea monogyra	Burrobrush (jecote)	September-November	–
Hymenoclea salsola	White burrobrush	April-June	–
EUPHORBIACEAE			
Ricinus communis	Castor bean	April-November	+
GRAMINEAE			
Cynodon dactylon	Bermuda grass	February-November	++
Sorghum halepense	Johnson grass	March-October	++
PLANTAGINACEAE			
Plantago insularis	Indian wheat*	February-May	+
POLYGONACEAE			
Rumex crispus	Curly dock*	April, May	+
Rumex hymenosepalus	Canaigre*	April, May	–
MISCELLANEOUS TREES			
Cupressus species	Cypress	December-May	+
Fraxinus velutina	Arizona ash	February-April	+
Juniperus species	Juniper	October-January	–
Morus species	Mulberry	March-May	++
Olea europaea	Olive	April, May	++
Populus fremontii	Cottonwood	January-March	++
Ulmus species	Elm	February, March	–

*Names taken from Kearney and Peebles: *Arizona Flora*.[15]

†Symbols denoting relative abundance of plants: ++ = Abundant. + = Common. – = Sparse.

Listed below are the important fungi found in the Phoenix area and the months in which they sporulate.

Scientific Name	*Common Name*	*Time of Sporulation (Inclusive)*
Acrothecium species	None	September-November
Alternaria species	None	January-December
Helminthosporium species	None	January-December
Homobasidiomycetes	Mushrooms	September-December
Hormodendrum species	None	February-December
Sphacelotheca holci	Johnson grass smut	January-December
Stemphylium species	None	January-December
Trichageum species	None	March-May, September, October
Uredinales	Rusts	January-December
Ustilago cynodontis	Bermuda grass smut	February-November

A number of anemophilous plants, especially grasses, were not listed as important allergenic contributors. These plants are either too sparse or they have been shown to be insignificant in the amospheric study. Some of these plants, however, may cause pollinosis in a susceptible person if there are large

TABLE II. MONTHLY AND YEARLY TOTALS
TEMPE, ARIZONA

SCIENTIFIC NAME	1957 JUNE	JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER	1958 JANUARY	FEBRUARY	MARCH	APRIL	MAY	TOTAL	PER CENT
						Pollen Grains per Cubic Yard of Air								
Amaranthus palmeri	3.2	13.9	77.1	283.5	63.0	2.4						9.6	452.7	4.5
Atriplex species	7.4	21.0	57.2	102.6	15.5	0.8					1.5	2.8	208.8	2.0
Beta vulgaris	12.2										1.6	34.5	48.3	0.5
Chenopodium species and miscellaneous chenopods			2.2	24.9	4.0	6.8	1.6	2.4		4.3	8.2	0.8	55.2	0.5
Salsola kali	2.1	0.9	16.8	6.3	3.6	1.2						6.6	37.5	0.4
Sarcobatus vermiculatus		2.7	4.0	5.4									12.1	0.1
Dicoria canescens				0.6	19.1	0.8							20.5	0.2
Franseria species		2.8	3.2	29.3	53.1	14.3			23.7	261.7	1,066.0	139.6	1,593.7	15.9
Hymenoclea species				8.0	23.8						100.6	48.5	180.9	1.8
Cynodon dactylon	54.9	67.1	32.5	32.0	25.8	5.1	1.3		5.1	28.0	131.1	171.3	554.2	5.5
Sorghum halepense	3.3	6.3	4.4	24.6	3.9					5.6	13.4	5.6	67.1	0.7
Plantago species										22.0	54.1		76.1	0.8
Rumex species										0.7	4.6	0.6	5.9	0.06
Cupressus-Juniperus				5.9	3.2	51.2	329.7	288.7	128.3	50.7	175.7	47.4	1,080.8	10.7
Fraxinus velutina									77.2	183.2	10.8		271.2	2.7
Morus species									3.0	3,674.0	1,068.6	24.0	4,769.6	47.2
Olea europaea										6.6	107.4	218.1	332.1	3.3
Populus fremontii								31.8	229.3	35.8	0.9		297.8	2.9
Ulmus species										41.7	0.6		42.3	0.4
						Pollen Grains per Square Centimeter per Slide								
Pinus species						1.2			1.6	7.1		23.1	33.0	
Prosopis juliflora											23.2		23.2	
Ricinus communis	0.8	0.4		5.1	3.0	12.4	3.6				2.8	5.7	33.8	
Miscellaneous grass	8.2	7.9	7.4	1.1	1.6				5.2	10.7	5.6		47.7	
Miscellaneous	3.5	2.5	0.4	1.2	1.0	15.2	9.2	12.3	10.1	8.8	21.3	5.3	90.8	

Pollen Index

$$\text{Pollen index}^{17} = \frac{1594}{200}(\text{season total}) + 20\left(\begin{matrix}\text{number of days with}\\ \text{count over 25}\end{matrix}\right) + \frac{85}{100}(\text{highest single count}) = 28.7.$$

isolated stands near the person's home or place of employment. The following is a list of these locally important contributors.

Scientific Name	*Common Name*	*Time of Pollination**
AMARANTHACEAE		
Amaranthus fimbriatus	Pigweed	June-September
Amaranthus graecizans	Tumbleweed	June-September
GRAMINEAE		
Bromus species	Brome grass	March-October
Distichlis stricta	Salt grass	March-October
Phalaris species	Canary grass	March-October
Poa species	Bluegrass	March-October
Sorghum sudanensis	Sudan grass	March-October
POLYGONACEAE		
Rumex conglomeratus	Clustered dock	April, May
MISCELLANEOUS TREES		
Acacia farnesiana	Sweet acacia	March-May
Carya pecan	Pecan	April, May
Pistacia species	Pistachio	April
Platanus species	Sycamore	April, May
Prosopis juliflora	Mesquite	April, May
Salix gooddingii	Willow	March, April

*All months shown are inclusive of time of pollination.

Atmospheric Survey.—Tables II, III and IV list monthly and yearly totals of all pollen grains and fungous spores counted. At the end of Tables II and III the pollen index for Franseria species was calculated as specified by the American Academy of Allergy and outlined by Durham.[17]

Because of the difficulty in differentiating the species of pollen grains in certain genera, it became necessary to report these species together under their respective genus. *Allenrolfea occidentalis, Bassia hyssopifolia,* and *Suaeda torreyana* are included in the category "*Chenopodium* species and miscellaneous chenopods," as the pollen grains all appear morphologically similar to those of *Chenopodium* species. The same is true for the nearly identical pollen grains of *Cupressus* species and *Juniperus* species, which have been combined. No attempt was made to differentiate the species of fungous spores. The spores of the fleshy fungi were labeled mushroom spores, and the rust spores were listed under the order Uredinales.

*Climatologic Data.**—The climate of the metropolitan Phoenix area is considered subtropical, with an average mean temperature ranging from 53° F. in the winter to 87° F. in the summer and a 28° F. average diurnal temperature variation. Although considerable irrigation water flows through the valley, the dry air is not easily saturated and the average mean relative humidity is a low 43 per cent saturation. Precipitation occurs chiefly during two parts of the year. There is a primary maximum fall during the summer months, from June through September, consisting of rains that are local in character; a second maximum fall comes during the winter season, December through March, resulting from a general storm movement from the northwest. Little precipitation occurs during the vernal and autumnal seasons. The average total annual rainfall is approximately 7.5 inches. Winds are predominantly

*Climatologic data obtained from United States Department of Commerce Weather Bureau local summary, Phoenix, Arizona.

TABLE III. MONTHLY AND YEARLY TOTALS
PHOENIX, ARIZONA

SCIENTIFIC NAME	1957 JUNE	JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER	1958 JANUARY	FEBRUARY	MARCH	APRIL	MAY	TOTAL	PER CENT
Pollen Grains per Cubic Yard of Air														
Amaranthus palmeri	8.4	7.0	66.4	115.1	61.7	3.7	0.6						262.9	5.3
Atriplex species	17.8	8.9	113.0	92.5	37.3	2.5	0.8			1.6		2.1	276.5	5.5
Beta vulgaris	5.8									2.5	4.2	50.7	63.2	1.3
Chenopodium species and miscellaneous chenopods		1.7	1.2	17.5	10.8		0.3	0.3	2.4	5.6	1.7		41.5	0.8
Salsola kali		0.6	1.2	3.6	13.7		1.2				1.2	5.4	26.9	0.5
Sarcobatus vermiculatus				13.9									13.9	0.3
Dicoria canescens													0	
Franseria species	3.3	1.2		22.1	52.0	8.5	1.3	10.3	26.2	154.5	590.0	105.0	974.4	19.6
Hymenoclea species					19.8					4.5	53.9	1.5	79.7	1.6
Cynodon dactylon	56.6	22.6	19.7	46.0	24.5	1.5	1.9			31.3	95.7	102.7	402.5	8.0
Sorghum halepense	10.8	3.6	6.2	14.2	3.0	0.4				3.2	4.8	8.9	55.1	1.1
Plantago species								6.2	22.8	48.1	3.5		80.6	1.6
Rumex species									0.9	16.8	4.9	5.7	28.3	0.6
Cupressus-Juniperus				2.8	3.0	18.8	247.6	128.8	132.4	67.0	129.6	31.5	761.5	15.3
Fraxinus velutina								1.2	151.4	737.2	6.0		895.8	18.0
Morus species										664.5	38.1		702.6	14.4
Olea europaea											29.6	141.5	171.1	3.4
Populus fremontii								36.3	89.3	6.5			132.1	2.6
Ulmus species										6.7			6.7	0.1
Pollen Grains per Square Centimeter per Slide														
Pinus species								0.3		5.3		20.2	25.9	
Pistachia species										19.6	33.4		53.0	
Prospois juliflora										6.2	15.1		21.3	
Ricinus communis		0.4			1.4			1.0	0.4				3.2	
Miscellaneous grass		11.7	2.5						3.6	6.5	4.9		29.2	
Miscellaneous	2.8	6.8	10.8	9.1	20.3	2.0	6.4	21.3	7.8	27.7	31.9	21.3	168.2	

Pollen Index

Pollen index[17] $= \frac{974}{200}$ (season total) + 11 $\left(\begin{matrix}\text{number of days with} \\ \text{count over 25}\end{matrix}\right) + \frac{65}{100}$ (highest count) = 16.5.

TABLE IV. MONTHLY AND YEARLY TOTALS

SCIENTIFIC NAME	FUNGOUS SPORES PER SQUARE CENTIMETER PER SLIDE												TOTAL	PER CENT
	1957							1958						
	JUNE	JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER	JANUARY	FEBRUARY	MARCH	APRIL	MAY		
Tempe, Arizona														
Acrothecium species				3.7	4.8	3.2	2.0						13.7	0.5
Alternaria species	10.2	38.3	50.0	49.8	301.9	380.8	143.0	130.3	105.2	114.3	88.7	62.6	1,475.1	58.3
Helminthosporium species	4.1	23.1	38.3	37.9	27.3	12.6	8.0	12.8	2.4	6.3	8.4	18.1	199.3	7.9
Hormodendrum species	0.6	2.1		5.5	104.3	5.6	5.6		20.8	18.8	13.0	9.0	185.3	7.3
Mushrooms		0.6		0.1	7.5	3.4	1.7						13.3	0.5
Sphacelotheca-Ustilago species	9.1	75.1	90.6	34.9	24.9	12.3	15.7	9.8	6.0	1.0	31.2	35.0	345.6	13.7
Stemphylium species	2.4	2.9	1.2	12.0	34.6	25.3	21.0	13.7	22.8	21.9	25.6	11.2	194.6	7.7
Trichagcum species	0.7			1.8	0.8					3.1	3.0	5.5	14.9	0.6
Uredinales	2.8	2.1	0.4	0.3	0.6	8.0	0.8	1.8	3.2	17.3	22.3	26.8	86.4	3.4
Phoenix, Arizona														
Acrothecium species				18.8	15.7	4.7	2.4	1.6		0.4		0.8	44.4	2.6
Alternaria species	12.3	27.1	26.5	21.1	198.4	218.6	116.4	107.0	66.9	42.5	24.2	30.6	891.6	52.6
Helminthosporium species	11.0	10.9	6.5	25.6	27.1	15.8	11.9	6.9	5.6	4.4	3.8	18.4	147.9	8.7
Hormodendrum species		1.0		1.9	6.4	8.4	2.2	0.4	3.8	4.2	7.6	2.8	38.7	2.3
Mushrooms				0.8	26.6	3.3	1.2						31.9	1.9
Sphacelotheca-Ustilago species	13.1	3.8	43.4	18.1	122.5	11.9	44.1	9.4	87.7	12.2	1.6	19.4	387.2	22.8
Stemphylium species		2.9	0.8	1.2	16.5	14.3	8.4	9.6	8.8	12.5	7.8	8.4	91.2	5.4
Trichagcum species									1.7	0.8		2.0	4.5	0.3
Uredinales	5.1			0.4	5.6	7.4	2.0	2.0		3.2	11.3	19.4	56.4	3.3

out of the east, with an average velocity of 5 m.p.h.; however, gales up to 40 m.p.h. have been recorded. Air turbulence and heat convection currents are responsible for vertical movement and a thorough mixing of atmospheric allergens. For these reasons, most of the pollen grains and fungous spores are caught in the morning and late afternoon hours. The average per cent of possible sunshine is 84 for the Phoenix area, although during the twelve months of this study it was 89 per cent, a very important factor in the production of pollen. In 1957 the average daily mean temperatures were 90° F. for the summer and 56° F. for the winter. This indicates a slightly warmer twelve months than normal. The average daily mean relative humidity was calculated to be 47 per cent, with an average daily maximum of 64 per cent daily at 5 A.M. and an average daily minimum of 30 per cent recorded at 5 P.M. each day. The total rainfall was found to be 8.2 inches, which is not much more than average; however, the month of September was unusually dry, with no precipitation, and the month of October had an unexpected 2.2 inches of rain. Because of this adversity, the temperature, precipitation, and relative humidity recorded during these two months were plotted on a graph (Fig. 1) along with the pollen grain count from the two stations in order to establish any possible relationship between climatologic factors and the concentration of atmospheric allergens. A conspicuous negative correlation is found between daily average maximum per cent relative humidity and the daily total pollen count per 2.42 square centimeters on a slide. There seems to be a general increase in number of pollen grains with a decrease in relative humidity, and vice versa. In order to substantiate this relationship, a scatter diagram (Fig. 1) was constructed, relating the relative humidity with total pollen counts. In addition to this, regression values were calculated and the coefficient of correlation was determined to be 0.967, which denoted a very close association. This relationship between relative humidity and pollen counts has been demonstrated experimentally by Shapiro and Rooks[16]; therefore, the present findings are merely supportive.

DISCUSSION

The metropolitan Phoenix area lies about 1,100 feet above sea level in the middle of the largest and most fertile valley in Arizona, the Salt River Valley. Desert mountains surround this valley on all sides, with the exception of the southeast, giving the impression of a large oval amphitheater, roughly forty miles long and twenty miles wide. The Salt River contributes most of the very important and much needed water for the valley, entering from the east out of the Arizona Highlands. Water storage and irrigation are regulated by a number of dams constructed on the river. This regulation, beginning with the completion of Roosevelt Dam in 1911, has resulted in a very large and efficient irrigation system controlled chiefly by the Salt River Valley Water Users Association. The Salt River Project irrigates 240,000 acres of highly developed agricultural land. In addition to this, 95,000 acres are under irrigation controlled by other projects in the valley.

Two general categories of plants contribute atmospheric allergens in the Phoenix area. One group includes the mesophytic species which are dependent to a great extent on the presence of water and, for that reason, are limited to

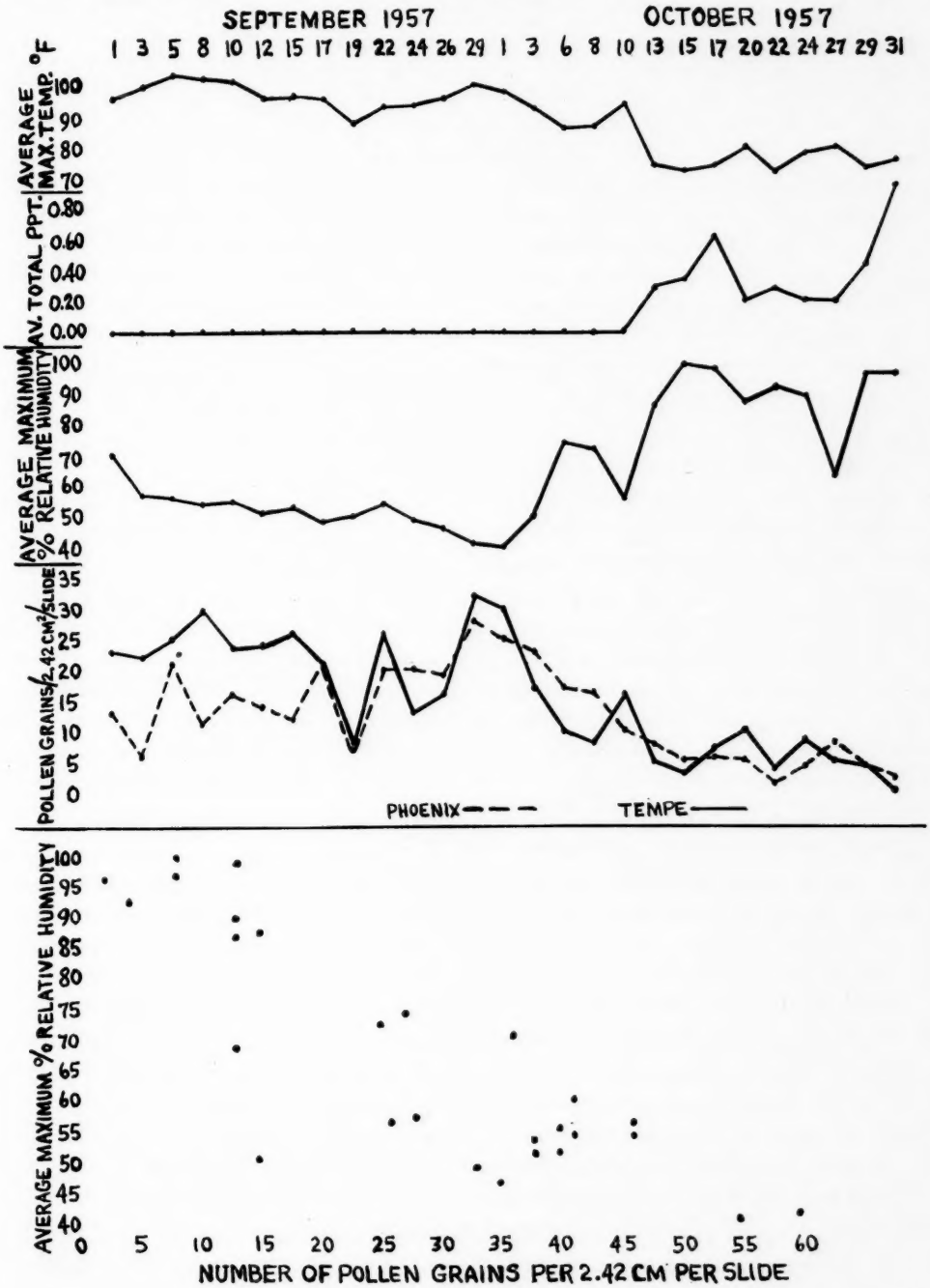
SEPTEMBER 1957
OCTOBER 1957
1 3 5 8 10 12 15 17 19 22 24 26 29 1 3 6 8 10 13 15 17 20 22 24 27 29 31
AVERAGE MAX. TEMP. °F
AV. TOTAL PPT.
AVERAGE MAXIMUM % RELATIVE HUMIDITY
POLLEN GRAINS/2.42 CM²/SLIDE
PHOENIX
TEMPE
AVERAGE MAXIMUM % RELATIVE HUMIDITY
NUMBER OF POLLEN GRAINS PER 2.42 CM PER SLIDE

Fig. 1.—Comparison of counts with climatologic data.

irrigated and cultivated areas. The second group includes the native xerophytic vegetation of the desert areas. Within each of these groups there are plants which can be classified as short-term pollinators, assuming importance briefly during the year, and there are others which shed pollen over a much longer period of time.

As mesophytic plants, most of the trees in the metropolitan Phoenix region are restricted to sites along water courses, and canals and in adequately watered residential areas. In general, the trees are short-term anemophilous pollinators, exhibiting definite seasonal periodicity in the production of pollen. Furthermore, a definite sequence is evident in the appearance of pollen from various tree species, although there is an overlapping from one to the other.

The first tree to reach anthesis is *Populus fremontii* Wats., the cottonwood, which is a very common tree native to the Salt River Valley. The pollination period is of short duration, usually extending from the middle of January to early March.

Fraxinus velutina Torr., the Arizona ash, is the next to shed its pollen, beginning about the first of February and continuing until the first of April. It is of secondary importance as a contributor to atmospheric pollen concentrations. (It may be noted in Table III that the Arizona ash pollen was extremely high in the Phoenix count, probably because of two very large ash trees near the sampling device.)

Toward the middle of March, the mulberry trees (*Morus* species) begin to pollinate, surrendering great quantities of pollen throughout April. The "male" mulberry has become the most popular shade tree in the valley, and counts of over 400 grains per cubic yard of air have been recorded at the Tempe station. However, these large counts were probably due to the many mulberry trees planted on and around the campus of Arizona State University. The Phoenix counts were much lower, and the botanical survey of that area revealed fewer mulberry trees. At any rate, *Morus* species can be considered first in concentration of atmospheric pollen grains under the class of short-term pollinators in the valley.

Olea europaea L., the olive tree, is the last of the short-term pollinating trees, blooming from early April until the end of May. This species is common in the valley, where it has been introduced for commercial and landscaping purposes. The "heavy" pollen of *Olea europaea* is transported largely by insects, but it is produced in such quantities that much of the pollen becomes wind-borne and, therefore, is considered an important allergen. The atmospheric concentrations of pollen from the olive trees are approximately equal to those of Arizona ash, although they appear at different times.

Certain conifers are important sources of pollen during the fall and winter months, and because their pollen grains are morphologically similar they are reported together in this study as a single group of long-period pollinators. Toward the end of September, *Juniperus horizontalis* Moench. and various other horticultural varieties of juniper begin to release pollen. Their period of pollination is overlapped by that of the native cypress, *Cupressus arizonica* Greene and the exotic Italian cypress, *Cupressus sempervirens* L. These cypress

trees begin to shed pollen in small amounts in December, increasing their production sporadically throughout the winter and spring months. Both species are popular landscaping trees in the metropolitan area.

One of the most important sustaining pollinators of the irrigated land is Bermuda grass, *Cynodon dactylon* (L.) Pers. This grass is used for most of the lawns in the Phoenix region and is present on most pasture land and moist areas of the Salt River Valley. An extremely hardy grass, it usually begins pollination around the last of February and reaches its peak in April and May. Its pollen remains constant at a lower level through the summer and early fall and finally decreases to negligible amounts in November. In the frost-protected areas along the periphery of the Salt River Valley, however, Bermuda sheds pollen all year.

The only other specific grass considered in this study was *Sorghum halepense* (L.) Pers., known as Johnson grass. Although it is large and conspicuous along roadsides, irrigation canals and cultivated fields, it does not shed much pollen. As Phillips[8] describes Johnson grass, "Its pollen output does not correspond to its bulk." Contributions from the remainder of the grasses found in the valley were listed as miscellaneous grass pollen, since they were difficult to differentiate and were present in very small amounts.

Amaranthus palmeri Wats., commonly known as careless weed or Palmer's amaranth, rates special consideration among the mesophytic hay fever plants dependent upon cultivation. This herbaceous annual is abundant on irrigated land and along roadsides, washes, and canals and is particularly concentrated in citrus groves, where it is grown as a cover crop. Its pollen begins to appear around the first of May and becomes quite abundant in late summer and early fall. During the month of September, at the Tempe station, a total count of 283.5 pollen grains per cubic yard of air was recorded, establishing this plant as the most important early-fall pollinator.

The xerophytic flora of the deserts and arid mountains, which comprise a large portion of the Salt River Valley and surroundings, includes several important anemophilous plants. The dominant hay fever plants are the several species of the genus *Franseria*. These are the desert false ragweeds or the bur sages.

The principal contributor of atmospheric allergens in this genus is *Franseria deltoidea* Torr., the rabbit bush, one of the climax plants in the desert plant succession. This perennial shrub is the worst offender in causing hay fever from the last of February through May. A less abundant perennial, *Franseria dumosa* Gray, the desert ragweed, pollinates in the spring and has been observed to pollinate again in the fall in some areas of the valley. Another spring pollinator belonging to this genus is *Franseria ambrosioides* Cav., the canyon ragweed, usually found in moist depressions on the desert or along roadsides and canals. A fourth species, *Franseria confertiflora* (DC.) Rydb., the slender ragweed, is not a desert inhabitant but should be mentioned here. This herbaceous plant grows rank in the late summer and fall along canals and irrigated fields and is responsible for pollen sensitivity from late August through

November. The pollens of the four Franseria species are morphologically indistinguishable, and no attempt was made to differentiate them.

The members of *Franseria,* as a group, were found to be the greatest contributors of atmospheric pollen, excluding the trees, during February, March, and April at both sampling stations. They also claimed first position at the Phoenix station during the month of May. (Bermuda grass was more concentrated during May at the Tempe station.) The pollen index for *Franseria* species was calculated for each station. (Tables II and III.) The index for the Tempe area during the period from June 1, 1957, through May 31, 1958, was 28.7, and the index for the Phoenix area during the same period was 16.5. These indices are to be compared with the previously reported index of 0.21 for the Phoenix area, as reported in the JOURNAL OF ALLERGY.[18] The last figure was derived from studies made during the fall only, when the pollen concentrations of Franseria are at their lowest.

The true ragweeds of the genus *Ambrosia,* which pollinate in the fall, are not found in the valley and, for this reason, the metropolitan Phoenix area has acquired the reputation of being a hay fever-free resort. Phillips,[6] however, found that persons susceptible to the allergenic reactions of *Ambrosia* have nearly a 50 per cent chance of being affected by *Franseria* their first season in the valley, and many more will become sensitized following exposure.

Some other important anemophilous plants of the desert also belong to the composite family, as do the false ragweeds. These are two species of Hymenoclea, burrobrush, and *Dicoria canescens* Gray, a fall pollinator of less importance. *Hymenoclea salsola* Torr. and Gray, a spring pollinator, contributes more pollen to the atmosphere than *Hymenoclea monogyra* Torr. and Gray. The latter is very conspicuous along roadsides and river beds during the fall when it pollinates.

The genus *Atriplex,* the saltbushes, includes another very important group of xerophytic hay fever plants. The first to appear is *Atriplex elegans* (Moq.) Dietr., scattered sporadically all over the valley and pollinating during April and May. *Atriplex wrightii* Wats., the annual saltbush, appears later, shedding a considerable amount of pollen through the summer and early fall months. Three perennial shrubs—*Atriplex lentiformis* (Torr.) Wats., *Atriplex canescens* (Pursh) Nutt., and *Atriplex polycarpa* (Torr.) Wats.—also pollinate during this period. All five species were counted and recorded together as one group, *Atriplex* species. The pollen counts for members of this genus were higher at the Phoenix station than at the Tempe station. These are halophytic plants and are indigenous in this region to the alkaline soils of the Salt River Valley.

Several other representatives of the Chenopodiaceae family, in addition to *Atriplex,* are important pollen-producing plants in the Phoenix area. Many of these are living on the wide river bottom of the Salt River, which has been left with no surface flow because of the impoundments upstream. *Sarcobatus vermiculatus* (Hook.) Torr., *Allenrolfea occidentalis* (Wats.) Kuntze, *Suaeda torreyana* Wats., several species of *Chenopodium,* and *Salsola kali* L. are conspicuous members of this plant community.

Salsola kali L., the Russian thistle or tumbleweed, has become established on great areas of wastelands, fallow fields, and vacant lots in the valley. In spite of this, the total pollen released by Russian thistles in this region is negligible when compared to that produced in other parts of Arizona and the other western states. Another plant which closely resembles Russian thistle is *Bassia hyssopifolia* (Pall.) Kuntze, smother weed. It and a few mesophytic species of *Chenopodium* are commonly distributed along irrigation canals and roadsides in the valley.

Several plants were of minor importance as sources of air-borne pollen. These belonged to several different ecologic and taxonomic groups. Species of *Plantago,* plantain or Indian wheat, blanket large areas of the desert and contribute to the atmospheric allergens in the early spring. Also the docks, *Rumex crispus* L. and *Rumex hymenosepalus* Torr., shed pollen in small quantities during the spring. The former, called curly dock, is found only in moist places, but the latter occurs in somewhat drier areas in sandy soil. Attempts have been made to grow *R. hymenosepalus,* known as canaigre, for its tannin content.

A successful commercial crop plant grown in the valley is the sugar beet, *Beta vulgaris* L. It is grown for production of seed, and a few thousand acres are harvested yearly. The plants reach anthesis in April and are pollinating at their maximum in May. The seeds are then harvested in June. The pollen counts for this species were greater at the Phoenix station than at Tempe.

Three other minor allergens recorded in this study were pollen grains from *Ricinus communis* L. (castor bean), *Prosopis juliflora* (Swartz) DC. (mesquite), and *Pistacia* species (pistachio). These were unimportant because of the small amount of pollen shed and, in the case of pistachio trees, the sparse distribution.

The pollen grains of *Pinus* species were recorded on several occasions. According to Wodehouse,[19] pine pollen is not an important allergen, but Rowe[20] has demonstrated it to be a source of allergies even though reported cases have been rare.

Finally, those pollen grains that could not be identified were labeled "miscellaneous." At least a part of these were pollen grains from entomophilous plants and atypical forms from anemophilous species. It may be noted that an unusually large number of unidentified pollen grains were recorded during the winter months. Many of these were morphologically similar and might have been produced by plants of one genus or species. It is my conviction that, because of their atmospheric incidence, these should be investigated further as possible allergens.

Fungous spores from several species were observed, but only those which positively could be identified by microscopic examination were recorded. Such spores as those from species of *Penicillium, Aspergillus,* and *Rhizopus* could not be discerned on the exposed slides. It is believed, however, that they are always present and ubiquitous, for the colonies are generally formed upon exposure of proper media to the air.

Spores of *Alternaria* species were undoubtedly the most concentrated, constituting over 50 per cent of all the spores counted at both stations. It is of particular interest that the heaviest concentration of *Alternaria* spores, as well

as most of the other spores recorded, were found during the late fall and winter months, which is not always the case in other parts of the country. Another interesting result is the year-long concentration of smut spores contributed mainly by smut of Johnson grass, *Sphacelotheca holci* Jackson, and to a lesser extent by smut of Bermuda grass, *Ustilago cynodontis* (Pass.) Curzi.

The report of the occurrence of the fungous spores is merely a preliminary study; more complete and detailed investigations involving culturing methods are necessary. However, a general picture of the seasonal distribution and concentration of fungous spores has been developed on the basis of examination of exposed slides.

Although the concentrations were predominantly higher at the Tempe station, there was a good agreement in the seasonal occurrence of the pollen grains and fungous spores at both stations. One should not conclude, however, that Tempe will necessarily always have a greater concentration of atmospheric allergens than downtown Phoenix.

Another important point is that at no time were there any pollen grains recorded from species of *Quercus* (oak) or *Artemisia* (sage), although these plants are found in abundance at higher elevations to the north and east of the valley. Therefore, there is no evidence that allergens from outside the valley are contributing to the hay fever problem in the Phoenix area.

In comparing the local counts with those of other areas in the United States, it is evident that the summer and fall counts are below average, although spring counts are about as high as those of other sections of the United States. The winter fungous spore concentration is of considerable consequence in the valley. Further investigation should be conducted, comparing these counts with subsequent studies in the Salt River Valley to determine more exact patterns of concentration and seasonal distribution of allergens. Also, more detailed differentiation of the pollen grains should be made, with special emphasis on the winter pollen, so that information will be available as to the presence of more specific allergens.

SUMMARY

1. A botanical survey of the hay fever plants in the metropolitan area of Phoenix, Arizona, is presented.

2. Data are given concerning the kind, concentration, and seasonal occurrence of the atmospheric pollen grains and fungous spores found during a one-year investigation conducted from June 1, 1957, through May 31, 1958, in Phoenix and Tempe, Arizona.

3. Morus species (mulberry) and *Fraxinus velutina* (Arizona ash) are found to be the most important tree pollinators contaminating the air in the spring. *Franseria* species (false ragweeds) and *Cynodon dactylon* (Bermuda grass) are heavy pollinators that reach anthesis in the spring and shed pollen sporadically through the summer and fall. (Contrary to popular belief, only one grass—Bermuda—was found to shed great enough concentrations of pollen to be considered significantly important as a general allergen.) *Amaranthus*

palmeri (careless weed) and *Atriplex* species (saltbush) are heavy contributors to the atmospheric pollen in the summer and fall months, the careless weed being the most important. Finally, the fungous spores are found in the air year round, with spores of *Alternaria* species the most prevalent.

4. It is concluded that a definite allergy problem exists in the Phoenix area and the Salt River Valley, as evidenced by the presence of allergens in the air throughout the year.

The cooperation and assistance of many persons too numerous to mention were necessary in conducting this investigation. I am particularly indebted to Dr. James A. McCleary for his inspirational guidance and advice during the course of this research and to the other members of my committee—Drs. Ronald R. Clothier, Edward E. Burgoyne, and Herbert L. Stahnke—for their criticisms and suggestions. I am also grateful to Dr. Charles W. Vivian and members of the Greater Arizona Chapter of the Allergy Foundation of America for their interest and consideration in this study. Finally, I wish to express my gratitude to Dr. Chester R. Leathers for his valuable assistance in the identification of the fungous spores and the editing of the manuscript.

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MORE STRESS ON EDUCATION IN ALLERGY

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AS ALLERGISTS, and always as physicians concerned with the future of medicine, we cannot help realizing the need for more emphasis on allergy in medical schools. This is a time of changing dimensions in medical science. It is accordingly a time for thoughtful review of the medical school curriculum. All over the country there is going on an elvaluation and upon its heels a revision of the courses of study. The latter must naturally be hesitant, responsible, and sure. What today's physicians are trained to know and to do cannot be grounded upon speculation and untried enthusiasms. That supremely important content must be built upon certainty, but upon altering and growing certainty, so the graduating student will have a broad base of knowledge in the ever-widening scope of medicine.

Dr. David B. Allman,[1] president of the American Medical Association, reports that "changes affecting every aspect of human life are occurring at an ever accelerating rate" and that "they have presented new problems and challenges to medicine and its allies as well as to other areas of activity." He also states that there is "sincere concern in regard to the education, training, and development of the personnel needed to meet and solve effectively the problems with which they will be challenged."

It is our responsibility as allergists to see that the revised and broadened curriculum includes teaching in the basic principles of allergy and related immunology. We should hope to accomplish two purposes. First, ev .y graduating physician should be well grounded in the basic principles of allergy so that he can recognize allergic manifestations when they present themselves. Our second aim should be to make the medical student conscious of allergy as an interesting and rewarding specialty so that there will be future allergists competent to carry on the expanding work.

Perhaps we should start with a joint committee on education of the American Academy of Allergy and the College of Allergists, one which can set up a continuing survey of undergraduate and postgraduate education in allergy. The data could be assembled as a base line and subsequently modified as conditions change.

Dr. Charles Marple[2] of the Allergy Foundation of America has suggested the possibility of a give-and-take arrangement in which data on existing conditions are collected and assistance and information are provided to permit the medical schools to improve their particular situations.

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In his report on a survey of graduate education in allergy for which the Foundation received grants in 1955 and 1956, Dr. Richard Kern[3] set forth a number of requirements for a survey of this kind:

1. It must have the facts on existing programs of education in allergy.
2. It must keep that information up to date.
3. It must publish that information annually in journals that will make it available to those seeking instructions.
4. It should verify the information by periodic visits of inspection by qualified allergists to the institutions active in such education and research.
5. It should give advice, constructive criticism, and encouragement, based on the knowledge of local programs, to help these institutions to achieve and maintain the highest standards.
6. It should seek ways and means for financial and other assistance in the interest of supplying an adequate number of allergists and of fostering sound programs of research.

While Dr. Kern made these suggestions in reference to graduate and postgraduate training in allergy, they could apply equally well to the survey of undergraduate education.

Supplementary to the Foundation survey of 1956, it might be well to take a look at the primary findings of the undergraduate study, as reported by Dr. Horace S. Baldwin[4]:

More than one-third of the medical schools had no lecture courses in allergy.

Only twelve of the seventy medical colleges had been approved for residencies and fellowships in allergy by the American Board of Medical Specialties.

Thirty-one medical schools had no funds available for research in allergy.

Thirty-four medical schools had increased instruction in allergy in the previous five years, but thirty-three had not.

Departmental teaching staff members specializing in the allergic diseases varied from none in four schools to fifteen in one. About half of the seventy institutions had three or more staff members specializing in allergy.

All but five of the schools had allergy clinics, and fifty-nine of the seventy used the clinics for teaching purposes. Most of the schools provided opportunities for working in wards or outpatient allergy clinics.

Dr. Baldwin reported on seventy medical colleges, but today there are eighty-five schools of medicine in the United States and Puerto Rico, as listed in the *Journal of the American Medical Association*. Examination of their catalogues reveals that only twenty-one mention courses in allergy. It can be

assumed that the sixty-four others have some teaching in allergy, but it is difficult to know how much or how little. At least the very catalogue reticence indicates small recognition of it. The important thing that stands out is that less than one-third of the schools consider allergy important enough to list in their offerings.

Dr. Kenneth Mathews[5] of the Research Council of the American Academy of Allergy made a comprehensive study of undergraduate education in allergy in 1958. When this is published, it should afford a clear view of the present status of allergy teaching and show just how belated is its recognition.

These surveys, which have been undertaken at the expense of so much time and effort, will be useless unless the results are employed to further education in allergy. A joint education committee composed of members of both societies could continue the surveys along the lines suggested by Dr. Kern and publish annual reports.

The next step, of course, would be to use the information for furthering the educational program. The committee could furnish assistance and information to the medical schools, but there will also be the necessity for individual effort. Most of us have teaching affiliations with medical schools through the staff, the allergy clinic, or the teaching hospital, and we can thereby promote better understanding of allergy at a personal level. The primary requisite for a successful undergraduate course in allergy is a sympathetic attitude by the dean of the medical school and by the professor of medicine of the school. It is essential to have their cooperation, support, and help.

First- and second-year students can begin the study of allergy during their courses in bacteriology, immunology, and physiology. The third-year student can be taught the basic fundamentals of the allergic response, with demonstrations and various laboratory experiments to illustrate these phenomena. The senior student should have an adequate number of hours in clinical allergy, where he can apply this basic knowledge. He should take histories, make examinations, skin-test, and treat cases under the supervision of a qualified allergist. There should be clinical conferences where students can present cases to the class for discussion.

The emphasis needs to be placed on the basic principles of allergy, for unless one has the basic understanding of the allergic response he is at a loss to explain the clinical manifestations.

The trend in medical teaching has been away from didactic lectures. My criticism of this is that students will have to spend too much time on assigned material. A lecturer can condense, interpret, and clarify this material. It is true that cutting down on lectures gives the student more hours in the clinic, but of what value is clinical application if the student has not fully absorbed the fundamentals? There should be a well-balanced program in both theory and practice. We must be careful to see that allergy has such a teaching program.

For a well-rounded program, there should be a full-time allergist on the staff. We should work toward the ultimate goal of such a full-time teacher

in each medical school. Dr. Hugh H. Hussey,[6] reporting on the changing dimensions of medical knowledge and their implications for medical education, research, and practice, has this to say:

> The chief development in the medical schools has been an increase in the number of full-time clinical teachers. For example, twenty-five years ago, in a medical school of modest resources and reputation, it was not surprising to find a department of medicine in which the director was the only full-time man. Today the picture is quite different. In that same school, the director is likely to have quite a large group of full-time people, representing areas of special clinical interest.

It is for us to see that our representative is there also. What allergy needs is to be needed.

In the past few years there has been much controversy concerning the quantitative content of the undergraduate medical curriculum and the necessity to reduce the tremendous amount of detailed information now deemed essential. Physicians, the men who have lengthened human life, have increasingly found their own lives too short for all they have to learn. We cannot go on adding to the years of their getting ready. We cannot in all conscience make it so that the student gets his diploma at a medical school commencement in the morning and collects his old-age annuities in the afternoon.

There have been many suggestions—shortening the premedical education, lengthening the course of study in medical school, extending the school year, concentrating on specialties during the last two years of medical school, and others. Duke University recently announced plans for a major educational program designed to produce physicians who are also skilled research scientists, and the University of Pittsburgh initiated an experimental program designed to permit a small number of students greater flexibility in their college and medical educational experience. Curriculum analysis and modification is the general trend in medical education.

Our chief concern should be that allergy is not neglected or shunted aside in this general revision of curriculum. Allergy is undeniably related to every province of medicine, and there is an overwhelming need for more knowledge and better understanding in the field, not just as a specialty but as an integrated part of the whole. It is our responsibility, singly and collectively, to see that allergy assumes its rightful place in the teaching of medicine.

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Medical Arts Bldg.

LEUKOCYTIC TRANSFER OF THE IMMEDIATE TYPES OF ALLERGIC REACTION IN MAN. II. THE CORRELATION OF LEUKOCYTIC TRANSFER WITH OTHER SENSITIVITY FACTORS

An Eight-Year Study on One Atopic Donor

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INTRODUCTION

THE passive local transfer of an immediate* wheal type of hypersensitive reaction in man with a suspension of venous blood leukocytes as the sensitizing medium was reported in 1950 by Walzer and Glazer.[1] The donors of the white blood cells were atopic patients, sensitive both clinically and by skin test to pollens and animal danders. The responses elicited by skin tests with allergens at the passive transfer sites were small in size and never exceeded a slight or one-plus (+) reaction. Leukocytic transfer failed in some instances, even though the donor's reaginic titer was high and his skin reactions were pronounced.

The unusual features of the phenomenon were at first attributed to the limitations of the technique. Particularly disadvantageous was the pronounced inflammation which developed at the site of the intracutaneous injection of the leukocytic suspension. To overcome this difficulty, an alternate transfer technique was devised employing an extract of shattered leukocytes as the sensitizing medium. The details of this procedure and a comparison of its merits and limitations with those of the cell-suspension method have been described in a previous communication.[2] Although the leukocytic extract technique materially reduced the inflammation produced by the sensitizing injection, it did not bring about an appreciable increase in the size of the passive transfer reaction.

In the development of the techniques, it proved advantageous to use some donors and recipients repeatedly. One such donor was D. G., whose history was related briefly in the previous report.[2] D. G., now 27 years old, has been treated by us for various allergic disturbances for the major part of his life.

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*In this, as in previous reports, the term "immediate" is employed to characterize the time of appearance rather than the immunologic mechanism mediating the allergic reaction. Although the sera of most of the donors studied contained skin-sensitizing antibodies, leukocytic transfer trials were also carried out in persons who manifested immediate whealing responses to tests with allergens but in whom no circulating antibodies could be demonstrated.

Because of our intimate knowledge of his case history and the peculiar pattern of his sensitivities, D. G. was used repeatedly as a donor of leukocytes for transfer studies. From November, 1950, to March, 1959, he served in this capacity on more than fifty different occasions. The findings in his case contributed much toward proving the specificity of the leukocytic transfer reaction.

D. G. was one of a series of donors with different types of immediate hypersensitive reactions being studied with the leukocytic transfer technique. As the studies progressed, the unusual findings in the case of D. G. convinced us of the advisability of presenting these data in a separate communication in advance of the report on the entire donor series. It was felt that the conclusions drawn from the detailed and carefully controlled experiments on D. G. might aid in the analysis and interpretation of the findings obtained in the less complete studies performed on other donors.[12] The fact that the decision to present a separate report on D. G. was reached relatively late in the course of these investigations will account for some of the obvious gaps in the data which appear in this communication.

CASE HISTORY OF D. G.

Because the leukocytic transfer experiments on D. G. dealt exclusively with his pollen sensitivities, only these aspects of his history will be presented in detail. Other phases of his allergic history will be mentioned briefly, but most of the voluminous medical record having no direct bearing on the immunologic problems under consideration will be omitted.

D. G. was born in the borough of Brooklyn, in the city of New York, in March, 1932. At the age of 20 months, he came under our observation with a history of asthma, atopic dermatitis, and allergic rhinitis, all of moderate severity, which started at the age of about 1 year. His family history was positive for atopy. His symptoms and physical signs and his nonimmunologic laboratory findings were typical and warrant no detailed description.

Preliminary skin testing by the indirect (serum passive transfer) method[3a] in May, 1934, and a more thorough study with the same technique, in March, 1936, revealed positive reactions to many allergens. Strongly positive reactions were obtained to pollens, legumes, nuts, seeds, cereals, fruits, and vegetables. Weakly positive transfers were obtained to feathers, wool, house dust, and other household inhalants. The reactions to meats, milk, egg, fish, animal danders, and molds were negative. A regime based primarily upon the elimination of contacts with troublesome inhalants and the avoidance of food offenders as revealed by the indirect tests and by daily diary studies brought about a rapid improvement in the patient's condition. His dermatitis soon ceased to be a problem. The asthma attacks diminished in frequency and severity. Because of the patient's rapid improvement, no hyposensitization treatment was needed. In 1938, when D. G. was 6 years of age, supervision of his case was discontinued.

In March, 1945, at the age of 13, D. G. returned for further observation, primarily because of his allergic rhinitis which had been particularly acute during the previous ragweed season. In the seven-year interval, his asthma attacks had remained infrequent and mild. He had developed a tolerance to most of the previously offending foods, but the ingestion of wheat and chocolate still produced rhinitis. Intracutaneous tests performed directly upon the patient produced weakly positive reactions to cereals, legumes, nuts,

TABLE I. SUMMARY OF POLLEN SKIN REACTIONS, SYMPTOMS, AND TREATMENT IN DONOR D. G. FROM 1944 TO 1959

	RAGWEED				TIMOTHY			TREES		ENGLISH PLANTAIN	
	SKIN REACTIONS*				SKIN REACTIONS*						
YEAR	0.001 MG.	0.01 MG.	SYMPTOMS	TREATMENT	0.001 MG.	0.01 MG.	SYMPTOMS	SKIN REACTIONS* 0.01 MG.	SYMPTOMS	SKIN REACTIONS* 0.01 MG.	SYMPTOMS
1944			+++	None			0				
1945	+±	+++	+	Preseasonal	+	+±	0	+	0	+	0
1946	++	++±	±	Perennial	+	++	0	+±	0	+	0
1947	+±	++±	±	Perennial	+	++±	0	+	0	+±	0
1948			±	Perennial			0				0
1949	++	++±	±	Perennial	+	+++	0	+	0	+	0
1950	++		±	Perennial	++	+++	0	+	0	+	0
1951			+	Perennial	+±	+++	0	+	0	+±	0
1952	+±		+	Perennial			0	+	0		0
1953	++±		±	Perennial	+++		0	+	0	+±	0
1954			±	Perennial			0		0±		0
1955	++		0	Perennial	++		0	+	±	+	0
1956	+	+++	0	Perennial	+±	+++	0	+±	+	++	0
1957	+	+++	0±	None	+±	+++	0	+±	+±	++±	0
1958	+±	+±	0	None	++±	+++	0	+	0	++	0
1959	+±	+++		None	+++			+		+	

Test injections were made with 0.01 ml. of extract.

Scale of skin reactions:

+++ = Marked.
++ = Moderate.
+ = Slight.
± = Faint.
0± = Doubtful.
0 = Negative.

Scale of symptoms:

+++ = Severe.
++ = Moderate.
+ = Mild.
± = Faint.
0± = Doubtful.
0 = None.

*Milligrams of total nitrogen per milliliter of test solution.

and household inhalants, all of which had been positive by indirect testing in childhood. D. G. showed a pronounced reaction to ragweed and weaker positive reactions to other pollens (Table I). On the basis of his history and skin reactions, treatment with ragweed was started at once and continued without interruption until the fall of 1956, when clinical symptoms attributable to this pollen were no longer recognizable.

At the present writing (March, 1959), D. G. is a well-developed 27-year-old adult. He is married and works as an instructor in physical education in the New York City school system. He now resides on Long Island in a home furnished, for the most part, with "allergen-free" materials. Failure to ad-

here to a diet free of foods to which he is still sensitive is undoubtedly responsible for his mild perennial symptoms of allergic rhinitis. His nasal mucous membranes usually appear pale and edematous, and his nasal smears, on repeated examination, have shown a high eosinophil content. He has no pulmonary or cutaneous symptoms, and at this time, he presents no other significant clinical or laboratory findings pertinent to this discussion.

METHODS AND MATERIALS

Pollen Extracts.—The extracts used in these studies were those routinely prepared in the Allergy Laboratory of the Jewish Hospital of Brooklyn.[4] The stock pollen extracts were made annually, usually in January, and were standardized according to their total nitrogen content. Dilutions were made with buffered saline. The ragweed extracts were made of a mixture of giant and dwarf ragweed pollens. The timothy pollen extract was chosen to represent the grass pollens. Since the potency of the stock extracts tended to fall off during the course of the year, fresh extracts (labeled "SP"), usually made only of dwarf ragweed, were prepared from time to time and employed for testing along with the stock test materials. The six-tree pollen mixture contained equal parts of ash, beech, birch, hickory, oak, and poplar pollen extracts.

TABLE II. POLLEN REAGIN TITRATIONS OF D. G. SERUM FROM 1950 TO 1959

DATE	RECIPIENT	RAGWEED SERUM DILUTION				TIMOTHY SERUM DILUTION			
		1:16	1:64	1:128	1:256	1:16	1:64	1:128	1:256
11/ 9/50	G.	+±	+			+	±		
4/10/51	W.	+	+		±	+	±		0
3/11/53	K. R.		+		±		+		0±
5/23/56	R.	+	0±		0	+	±		0
5/ 9/57	B.	±	0	0		+±	+	+	
5/ 9/58	K. R.	+	±	0±		+±	+	±	
3/ 9/59	W. A.	+	0		0	++	+		0

Sites prepared with 0.05 ml. of serum.
Sites tested with 0.01 ml. of extract containing 0.01 mg. nitrogen per milliliter.
Scale of skin reactions same as in Table I.

Cutaneous and Reaginic Titrations.—While under treatment, D. G. was tested routinely almost every year with fresh stock pollen extracts. Serial intracutaneous tests were performed with increasing concentrations of timothy, ragweed, English plantain, and the six-tree mixture in order to determine the dilution of each pollen which would produce a marked (+++) reaction (Table I). By means of these annual titrations, pronounced alterations in the degree or pattern of skin sensitivity to pollens were detected.

During the course of the leukocytic studies, titrations for reagins to timothy and ragweed pollens were made at intervals by the method of Coca and Grove.[5] Cutaneous sites passively sensitized with serial dilutions of the patient's serum were tested with pollen solutions containing 0.01 mg. N/ml. (Table II).

All of the direct and indirect tests made on D. G., as well as the serum titrations for reagins and all leukocytic transfer tests, were performed by the same investigator (K. B.). She also read and recorded the results of all such tests. Hence, the data on this patient were obtained over a period of twenty-five years by one observer. Her extensive experience in serum passive transfer techniques proved of inestimable value in the leukocytic transfer experiments. Since July, 1956, this investigator has prepared all of the leukocytic materials used in the studies on D. G. They had previously been made by a former collaborator (S. S.).[2]

Leukocytic Transfer Techniques.—The details of the techniques employed in the leukocytic transfer studies on D. G. have been described.[2] No blood samples for the procurement of leukocytes were drawn for a week following the therapeutic pollen injections which the donor was receiving at four-week intervals. Sites on the outer aspect of the recipient's arm were prepared by the intracutaneous injection into each site of 0.025 ml. of leukocytic suspension (usually 1:10 by volume in Tyrode's solution) or of 0.05 ml. of leukocytic extract (usually 1:4 in Tyrode's solution). From one to four sites were prepared on an arm. These sites were tested when the inflammation produced by the sensitizing injection had apparently subsided. With the extract technique, the interval between sensitization and testing was usually five days; with the suspension method, the interval varied from seven to twelve days. An intracutaneous test with approximately 0.02 ml. of allergenic extract was introduced at the sensitized site and was duplicated as a control on adjacent normal skin. Other controls included tests with buffered saline, physiologic saline, various nonrelated allergens, and special materials.

Recipients in Leukocytic Transfer Studies.—The recipients in the leukocytic transfer studies on D. G. included eighteen presumably nonatopic adults who had been carefully selected from a large number of volunteers because they had shown completely negative reactions to skin tests with concentrated (0.1 mg. N/ml.) ragweed and timothy pollen extracts. Of these recipients, fourteen were used only once or twice. Four others served on seven to fifteen different occasions during periods lasting up to six years.

Reading and Grading Reactions.—The reactions elicited with the leukocytic transfer techniques were graded on the basis of a previously described classification especially designed for this purpose.[2] Immediately prior to the test with allergen, the sites were read by inspection and palpation to detect any residual inflammation which might have persisted following the sensitizing injection. After testing, readings by inspection and palpation were taken on both the test and control sites.

In the special classification of reactions, which was made necessary by the relatively small size of the leukocytic transfer response to testing, a slight positive or one-plus (+) reaction consisted of a central wheal about 0.5 cm. in diameter with a surrounding erythema. A reaction only slightly less than this was designated as a plus-minus (±) positive. Erythema on or around the edematous area was not regularly present in this grade of reaction. When the presence of edema was barely perceptible by palpation, the reaction was

read as a negative-plus-minus (0±). Erythema was not a common component in this grade of reaction. When no change in edema or erythema resulted from the test, the reaction was recorded as negative (0). Pruritus was associated only occasionally with leukocytic transfer reactions.

It frequently became necessary to correct the readings at the test sites to take into account various nonspecific factors, such as the persistence of traces of edema at the sensitized sites or the irritative properties of certain experimental test materials which, in the concentrations used, did not yield completely negative reactions at the control sites. To facilitate corrections of this nature and to preclude bias on the part of the investigators, it seemed advisable to resort to a numerical system of marking reactions, similar to that which had been formulated in a previous study for recording fine differences between skin reactions produced by *direct* testing.[6] Values from 0 to 12 were assigned to various degrees of response between the completely negative (0) and the maximally positive (+) reactions. The size and induration of the central edematous area represented the main criteria upon which the reactions were graded, with some allowances being made for the amount, intensity, and distribution of the erythema and for pruritus when this element was present. The numerical value of the control was deducted from that of the transfer site, and the remainder was reconverted to one of the aforementioned symbols on the basis of the following scale of equivalence: Numerical values of from 0 to 2, inclusive, were covered by the negative symbol 0; values from 3 to 5, inclusive, by the symbol 0±; from 6 to 9, inclusive, by the symbol ±; and from 10 to 12, inclusive, by the symbol +. The use of a symbol rather than a number as a final value for the reaction made it possible to retain the grading system which had been employed in previous studies, thus providing uniformity in terminology for the entire series.

The reactions resulting from *direct* intracutaneous tests on *donors* and from the *serum* titration tests were graded according to the standards commonly employed in these procedures.[3]

Interpretation of Results.—A final reading of one-plus (+) which could be elicited on repetition (as either a + or ± reaction) was considered to be significant. A plus-minus (±) or weakly positive reaction was deemed significant if it had been adequately controlled and could be elicited repeatedly (though not necessarily invariably) on repetition of the test. A negative-plus-minus (0±) reaction was too small to be regarded as reliable evidence of transferred sensitivity. Only when it occurred repeatedly and was associated with definite one-plus (+) or plus-minus (±) reactions elicited by the same test on other sites did it receive any consideration.

POLLINOSIS HISTORY OF D. G.

Although serum passive transfer reactions to timothy and ragweed pollens were already positive in D. G. at the age of 20 months, recognizable hay fever symptoms did not develop until 1944, when he was 12 years old (Table I). In the spring of 1945, preseasonal treatment with weekly sub-

cutaneous injections of increasing doses of ragweed extract was started. At the end of that ragweed season, injections of from 0.025 to 0.1 mg. N were continued at four-week intervals. D. G. responded well to this therapy. In October, 1956, after he had been practically free of ragweed symptoms for two seasons, treatment was discontinued. Symptoms were barely noticeable in 1957, and none were experienced in 1958.

Starting in 1954, when he moved his home to the borough of Queens in New York City, D. G. began to have symptoms of hay fever which started early in May and ended the first week in June. These were caused by tree pollens to which he had shown positive skin reactions for many years. When he again moved his residence in February, 1958, this time to Commack, Long Island, these symptoms became negligible. No leukocytic transfer studies were attempted in connection with the tree sensitivity, since the concentrated tree extracts were found to be nonspecifically irritating in the skin of the recipients.

D. G. has never experienced any symptoms of grass pollen sensitivity, although he has shown markedly positive skin reactions and high reaginic titers to timothy pollen for many years (Table I). Nor did he show evidence of clinical sensitivity to English plantain pollen, to which he also reacted positively by skin test. His reactions to tests with mold spores were always negative.

CUTANEOUS REACTIONS TO TIMOTHY AND RAGWEED POLLENS

The results of skin tests with pollens in D. G. from 1945 to 1959 are recorded in Table I. For the graphic presentation of this feature (Fig. 1), the test readings obtained during this period with 0.001 mg. N/ml. dilutions of pollens were chosen because they had elicited reactions of + or ++ intensity in D. C. Reactions of this size had been found by Bowman[7] to be more suitable for purposes of comparison than those of larger dimensions.

Direct intracutaneous tests on D. G. in early childhood (1935 to 1938) had revealed weak and approximately equal reactions to grass and ragweed pollen extracts. From 1945 to 1950, ragweed produced the stronger reaction; after 1951, timothy induced the larger response. The cutaneous reactions to both pollens diminished after 1953, but the most recent readings seem to show an increasing reactivity to timothy.

REAGIN TITRATIONS FOR TIMOTHY AND RAGWEED POLLENS

In Table II are listed the titers for timothy and ragweed pollens in the samples of D. G.'s serum taken at intervals during the eight years of leukocytic transfer studies. Because of variations in the recipients and in the age and nature of the test materials, these data are subject to some limitations when employed for comparative studies. Nevertheless, the major fluctuations in the reagin titrations occurring during this period in D. G. are clearly discernible in Fig. 2. For this graphic presentation, the relatively weak (+)

readings elicited on sites prepared with the 1:64 serum dilution were selected for reasons previously noted.

When D. G. was tested by the indirect method in 1932 at the age of 20 months and again at 4 years, reagins for timothy and ragweed were already

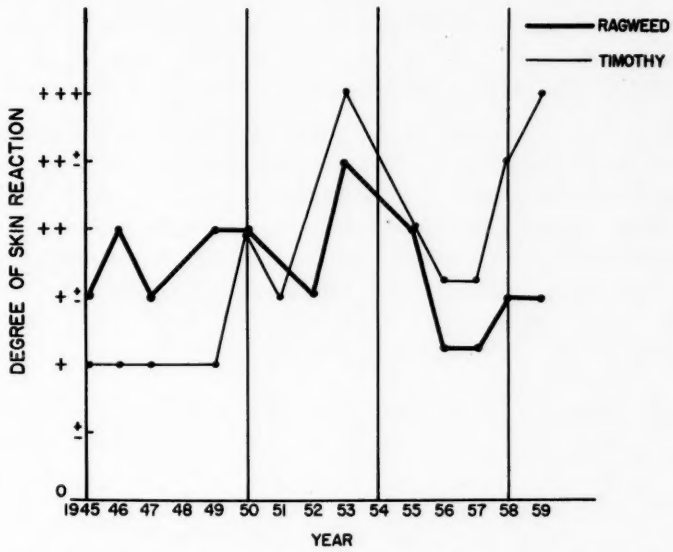

Fig. 1.—Reactions of D. G. to skin tests with pollens from 1945 to 1949. Dilution of test extract, 0.001 mg. N/ml. Amount injected, 0.01 ml.
Scale of positive reactions: + = slight; ++ = moderate; +++ = marked.

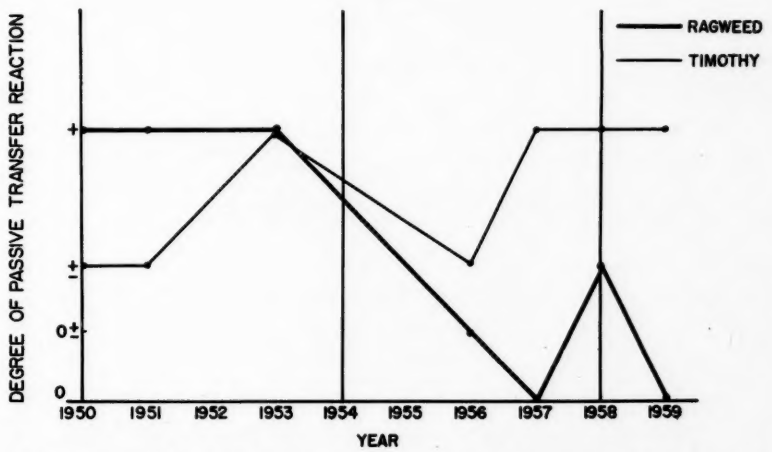

Fig. 2.—Titers of pollen reagins in D. G.'s serum from 1950 to 1959. Serum dilution, 1:64. Test extract, 0.01 mg. N/ml.
Scale of reactions: + = slight positive; ± = faint positive; 0± = doubtful positive; 0 = negative.

present in his serum, the latter in slightly greater concentration than the former. In 1950 the antibody titers for both pollens were greater than in childhood, with ragweed still the stronger of the two (Table II and Fig. 2).

In 1953, the readings with the 1:64 serum dilution were equal for the two pollens, but the 1:256 dilution tests still seemed to indicate a slight superiority for ragweed. In 1956 both reagin titers were diminishing, but at this time the timothy readings were greater than those for ragweed and they remained so thereafter. In the most recent titrations, the ragweed antibodies seem to be diminishing while those for timothy are gradually increasing.

ANNUAL ESTIMATES OF POLLEN SYMPTOMS

Estimates of the severity of the pollen symptoms in D. G. during each pollen season are listed in Table I along with his skin reactions for the same year. Because of the many specific and nonspecific factors which can influence hay fever symptoms, it proved to be extremely difficult to grade this component effectively. Fig. 3 represents a crude attempt to chart the severity of the patient's pollen symptoms from 1944 to 1958, inclusive.

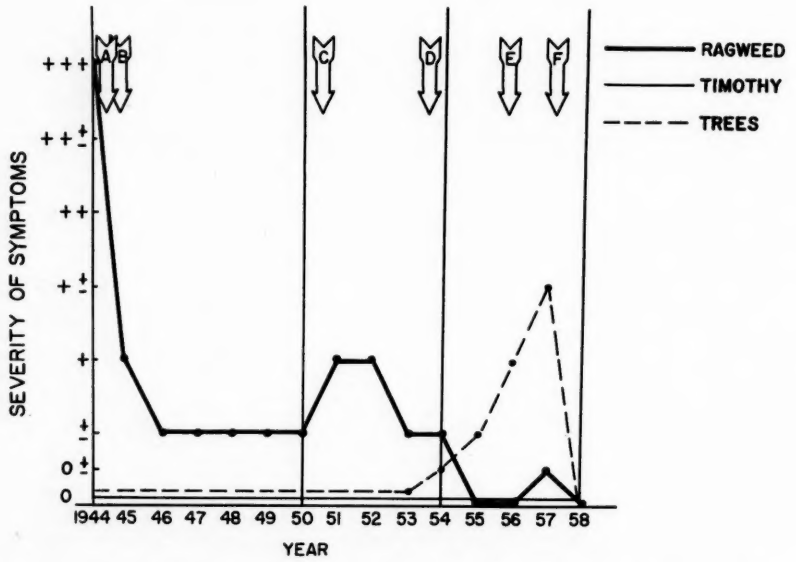

Fig. 3.—Severity of pollen symptoms in D. G. from 1944 to 1958. *A*, Preseasonal treatment with ragweed started in March, 1945. *B*, Perennial treatment with ragweed started in October, 1945. *C*, Changed summer residence in June, 1951. *D*, Moved his home to borough of Queens in New York City in April, 1954. *E*, Ragweed treatment discontinued in October, 1956. *F*, Moved his home to Commack, Long Island, in February, 1958.

Scale of symptoms: +++ = severe; ++ = moderate; + = mild; ± = faint; 0± = doubtful; 0 = none.

The ragweed pollen indices for New York City, computed annually in this laboratory from the daily ragweed pollen counts taken in this area,[8] were reviewed to determine whether any seasons of unusually heavy pollination had occurred from 1950 to 1958 which might have unduly influenced the severity of pollen symptoms in D. G. While the leukocytic transfer studies on D. G. were in progress, these indices seemed to have remained relatively constant. Annual variation in pollination was therefore considered insig-

nificant as a factor affecting the severity of this patient's symptoms during the course of these studies.

As a result of his ragweed therapy which had started early in 1945, D. G. experienced only mild symptoms that season and in subsequent years. In 1951 he started spending his leisure time during the summer months at Freehold, New Jersey, a community with a relatively high pollen index for ragweed.[9] For two ragweed seasons he was not quite as comfortable there as he was at his home in Brooklyn. In 1953 symptoms became mild again, even when he was at Freehold, New Jersey. In the spring of 1954 he married and changed his residence to the borough of Queens in New York City, where the pollen index was slightly higher than at his former home in Brooklyn. He nevertheless experienced only slight ragweed symptoms that fall and became practically symptom-free in 1955 and 1956. Because of this pronounced improvement, his ragweed treatment was discontinued in October, 1956. The next year very faint symptoms were occasionally noticed at the peak of the season in September, but the patient was completely free of ragweed symptoms in 1958.

The tree symptoms which D. G. began to experience in 1954 during most of May and the first week in June became progressively stronger each year (Table I and Fig. 3) until he moved away from this area in February, 1958. In the spring of 1958 he had negligible tree symptoms.

LEUKOCYTIC TRANSFER STUDIES ON D. G.

Leukocytic transfer experiments were started on D. G. in November, 1950. For several months only the suspension technique was used. After the extract method was developed, this became the preferred procedure. Throughout 1952 and 1953 the cells of D. G. were used repeatedly in a variety of studies. Then, except for an occasional trial in 1954, he was not tested again until April, 1956, when he was recalled in connection with another leukocytic transfer investigation. It was at this time that the loss of his leukocytic transfer potential for ragweed was discovered. Realizing the significance of this finding, we resumed leukocytic transfer tests with pollens.

Only part of the findings in the many studies made with D. G.'s cells are listed in Table III. Included there are the results of those experiments in which the standard techniques were employed or in which these procedures were modified in only minor detail. The experiments are listed in chronological order, with the suspension and extract techniques represented in separate sections of the table. The results obtained at each of the tested sites are recorded in Table III and are plotted in Fig. 4. As a result of the careful screening of recipients, the control reactions to pollens were almost always negative; for this reason, these readings were not listed in the tables. In the occasional instance when the control reaction was not completely negative, the reading at the transfer site was corrected accordingly. The listings in Table III, therefore, represent the final readings after all adjustments for nonspecific factors had been made.

TABLE III. RESULTS OF LEUKOCYTIC TRANSFER TESTS ON DONOR D. G. FROM 1950 TO 1959

SUSPENSION TECHNIQUE								EXTRACT TECHNIQUE									
			TIMOTHY		RAGWEED							TIMOTHY			RAGWEED		
DATE	EXPERIMENT NO.	RECIPIENT	ANTIGEN DILUTION (MG. N/ML.)	REACTION	ANTIGEN DILUTION (MG. N/ML.)	REACTION SITE 1	REACTION SITE 2	DATE	EXPERIMENT NO.	RECIPIENT	LEUKOCYTIC EXTRACT DILUTION	ANTIGEN DILUTION (MG. N/ML.)	REACTION SITE 1	REACTION SITE 2	ANTIGEN DILUTION (MG. N/ML.)	REACTION SITE 1	REACTION SITE 2
11/10/50	S1A	S. C.	0.1 SP	0	0.1 SP	+											
	S1B	G.	0.1 SP	0	0.1 SP	±											
2/13/51	S2A	G.			0.1	+	±	4/10/51	E5A	S. W.	1:6				0.1	+	
	S2B	G.			0.1	+	±								0.2	+	
3/ 6/51	S3	G.			0.1	+	±		E5B	W.	1:6	0.1	0	0	0.1	+	
3/20/51	S4A	G.			0.1	±		5/ 1/51	E7	S. W.	1:6	0.1	0		0.1	+	
3/24/51	S4C	G.			0.1	+						0.2	0		0.2	+	
5/23/51	S8	B.			0.1	0±		6/18/51	E11	W.	1:6				0.1	+	
					0.2	+									0.1 SP	+	
															0.1 SP	0±	
								3/ 4/52	E12A	S. W.	1:6				0.1	+	
									E12B	W.	1:6				0.1	+	+
								3/26/52	E15A	F.	1:6	0.1	0	0	0.1	+	±
									E15B	W.					0.1	+	
															0.2	±	
								4/ 7/52	E17	G.	1:5	0.1	0		0.1	±	+
								4/16/52	E19	S. W.	1:5	0.1	0		0.1	0±	
															0.2	+	
															0.1 SP	+	±
															0.2 SP	+	
								4/21/52	E20	G.	1:5	0.1	0		0.1	0±	
															0.1 SP	+	0±
								5/27/52	E28	G.	1:4				0.1	±	
															0.2	±	
															0.1 SP	±	
															0.2 SP	+	
6/ 9/52	S29	S. W.			0.1	+		6/ 9/52	E29	S. W.	1:4				0.1	0±	
					0.1 SP	+									0.1 SP	+	
															0.2 SP	+	

								4/ 8/53	E35	K. R.	1:4	0.1	0		0.1	±	
												0.2	0		0.2	+	
								4/30/53	E37	K. R.	1:4	0.1	0	0	0.1	+	+
								10/22/53	E38	K. R.	1:4	0.1	0	0	0.1 SP	±	
11/ 3/54	S43	K. R.	0.1	0	0.1	+	±										
4/10/56	S52	R.			0.1	0		4/10/56	E52A	R.	1:4	0.1	0±	0±	0.1	0	
									E52B	S.		0.1	0±	0±	0.1	0	
								5/16/56	E53A	K. R.	1:4	0.1 SP	0±	0	0.1	0	
									E53B	F. U.	1:4	0.1	0±		0.1	0	
								5/23/56	E54A	F.	1:4	0.1	0±		0.1 SP	0±	
												0.1 SP	0±				
								5/19/57	E55A	K. R.	1:4	0.1	0±		0.1	0	0
									E55B	S. I.					0.1	0	
								10/20/57	E56	K. R.	1:4	0.1 SP	0±		0.1 SP	0	0±
															0.2	0±	
3/ 8/59	S57A	K. R.	0.1	0±	0.1	0											
			0.2	0±	0.2	0											
	S57B	I.	0.1	0±	0.1	0											

Sites were prepared with 0.025 ml. of leukocytic suspensions in Tyrode's solution (1:10) or with 0.05 ml. of leukocytic extract.
Sites were tested with 0.02 ml. of antigen.
Scale of reactions is described in text.
SP = Freshly prepared extract.

Averages were computed for all of the readings obtained during each calendar year with each pollen. With these data, the leukocytic transfer results with the two pollens over the eight-year period were plotted in Fig. 4. The line between the ± and the 0± zones represents the point below which it becomes exceedingly difficult to gauge accurately any fine differences in the degree of reaction. For this reason, the data below this line were considered of limited statistical value, particularly as a basis for comparative analysis.

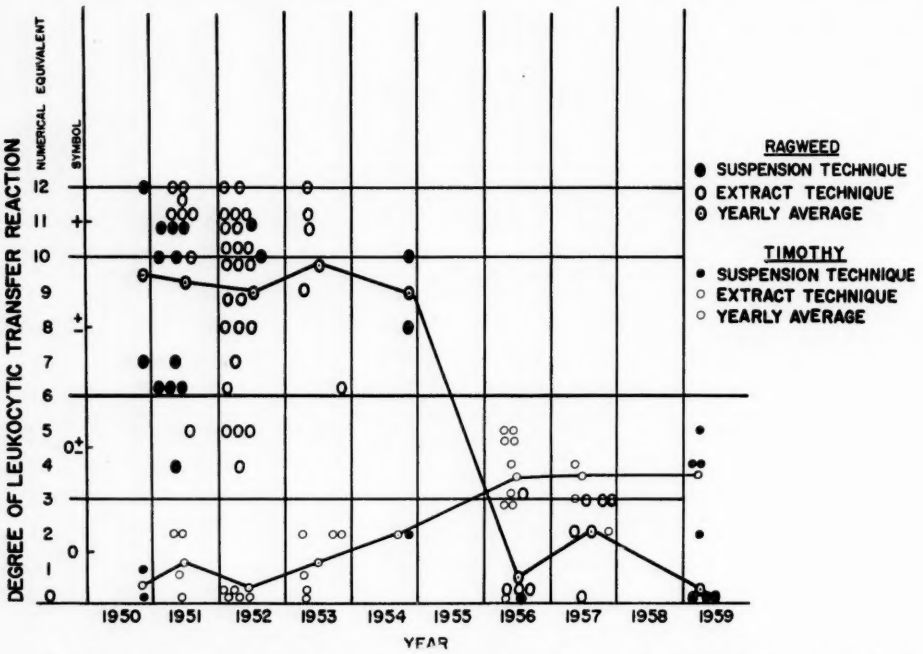

Fig. 4.—Results of leukocytic transfer tests with pollens in D. G. from November, 1950, to March, 1959. Yearly averages derived from results of all tests with both techniques. For scale of reactions, symbols, and numerical equivalents see discussion of "Reading and Grading Reactions" in text.

Results of Leukocytic Tests With Ragweed Pollen.—From November, 1950, to May, 1953, positive leukocytic transfers with ragweed pollen were obtained quite regularly with both techniques. In a single trial with the suspension technique in November, 1954, the result was still positive. When tests were resumed in April, 1956, after an interval of about seventeen months, only negative results were obtained with ragweed, although the same methods, the same technicians, and in some cases the same recipients were used. All subsequent trials with both techniques failed to produce another positive transfer to ragweed.

Results of Leukocytic Tests With Timothy Pollen.—At no time from November, 1950, to March, 1959, was a definite (+ or ±) transfer obtained with timothy pollen with either technique (Table III and Fig. 4). At the beginning, the results of tests with this pollen were completely negative. In recent years, however, zero-plus-minus (0±) reactions have been obtained repeatedly. Although reactions of this size may not be considered significant, their rela-

tively recent appearance and their repeated occurrence warrant continued observation of this reaction in the future.

CORRELATION OF LEUKOCYTIC TRANSFER WITH OTHER SENSITIVITY FACTORS

The negative result of the leukocytic transfer test for ragweed in April, 1956, came as a surprise, and explanations for this loss of transfer potential were sought. Upon investigation, it became apparent that at this time D. G. was also experiencing changes in his clinical symptoms, reagin titers, and

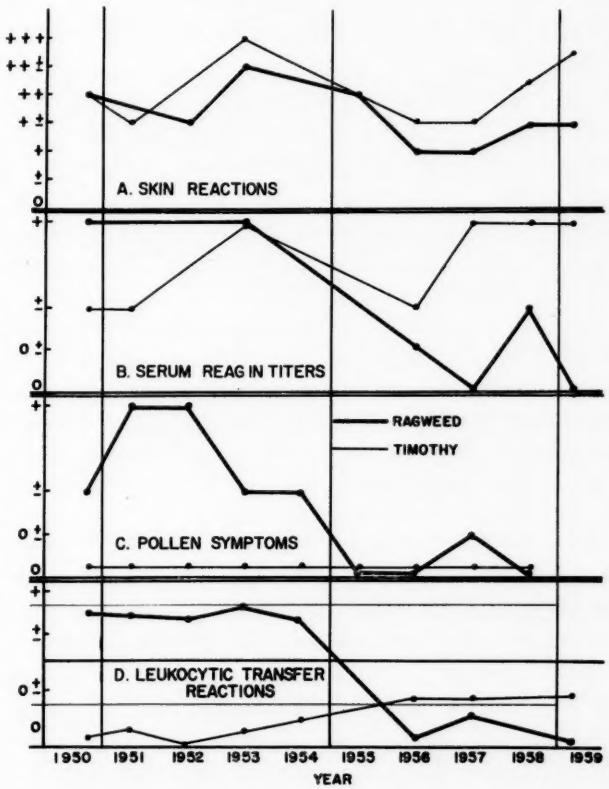

Fig. 5.—Correlation of skin reactions (*A*), serum reagin titers (*B*), severity of pollen symptoms (*C*), and leukocytic reactions (*D*), in D. G. from November, 1950, to March, 1959. (For symbols and scales see corresponding Figs. 1 to 4.)

cutaneous reactions to pollens. In view of these developments, the various data for the entire period were reviewed and the relationship of leukocytic transfer potential to other sensitivity factors was studied. The most important features of this analysis are presented herewith.

A. *Relationship of Leukocytic Transfer to the Degree of Cutaneous Sensitivity.*—

Ragweed: In the case of D. G., the results of the leukocytic transfer tests with ragweed might seem to bear some relationship to the intensity of the

cutaneous sensitivity to this pollen (curves *A* and *D*, Fig. 5). Positive leukocytic transfer tests with ragweed occurred only during the early years (1950 to 1954) while the skin reactions to this pollen were pronounced. Later, when the skin reactions became weaker, the transfer potential for this pollen was lost.

Timothy: The results of leukocytic transfer with timothy bore no relationship to the degree of cutaneous reactivity to this pollen. No definite transfers were obtained, despite the fact that for the major part of the eight-year period the skin reactions to timothy exceeded those to ragweed (Figs. 1 and 5, *A*).

B. *Relationship of Leukocytic Transfer to Reaginic Titers.*—

Ragweed: A comparison of the graphs representing the results of leukocytic transfer tests and of reaginic titrations over the eight-year period revealed a greater similarity between them than had been evident in the preceding comparison involving cutaneous sensitivity (Fig. 5, curves *B* and *D*). During the early years of this study, when the reaginic titers for ragweed were high, positive leukocytic transfers with this pollen were obtained regularly. With the decline in these titers seen in the later phases of the investigation, only negative results were obtained.

Timothy: As was the case with cutaneous sensitivity, the reaginic concentrations of the serum for timothy could not be correlated with the results of leukocytic transfer with this pollen. Despite the presence of serum antibody titers to timothy which were as high as or higher than those for ragweed during the major part of the eight-year period, a definite leukocytic transfer with timothy was never demonstrated.

C. *Relationship of Leukocytic Transfer to Clinical Sensitivity.*—

Ragweed: From 1950 to 1954, inclusive, the patient experienced typical symptoms of ragweed hay fever, although they were ameliorated to a considerable degree by therapy with this pollen. During these years the leukocytic transfer tests were regularly positive (Fig. 4 and Fig. 5, *C* and *D*). In 1955 and 1956 ragweed symptoms disappeared almost completely, although the pollen exposure factors remained unaltered. This clinical change was occurring in D. G. at about the time his leukocytes were losing their power to transfer sensitivity to this pollen. Ragweed symptoms were negligible in the fall of 1957 and were completely absent in 1958. The leukocytic transfer tests remained negative during this period.

Timothy: Throughout the entire eight-year period not a single definite positive leukocytic transfer was obtained with timothy, and at no time did D. G. manifest clinical symptoms of hay fever or asthma caused by this grass pollen.

The results of the leukocytic transfer test in D. G. were therefore unique in that they paralleled the clinical status of the patient with respect to both pollens. This was in obvious contrast to the findings obtained with direct and serum transfer tests in this patient. The latter tests could be correlated to a limited extent with symptomatology in the case of ragweed but not at all in the case of timothy.

THE SPECIFICITY AND NATURE OF THE LEUKOCYTIC TRANSFER REACTION

Because of the peculiar properties of the leukocytic transfer reaction, particularly its diminutiveness and variability in size at different sites on the same recipient, the need for adequate controls was imperative. Many routine and special methods of control were therefore employed.

The tests on leukocytic transfer sites were routinely duplicated on normal adjacent skin in the same manner as the control tests performed in serum passive transfer techniques.[3(a)] Any transfer test in which the control reaction was for any reason greater than a 0± was considered to be unacceptable for consideration.

Among the special control studies on D. G. was the attempt to transfer sensitivity to ragweed by the use of his erythrocytes processed in the same manner as his leukocytes.[1] Only negative results were obtained. Leukocytes from nonsensitive donors did not transfer sensitivity to ragweed or to any other common atopen.[1] In the case of D. G., the leukocytic transfer tests were negative with allergens, such as animal danders, to which he manifested no sensitivity either clinically or by skin test.

To rule out a nonspecific hyperresponsiveness of the type occasionally seen at serum-sensitized sites,[10] leukocytic transfer sites were tested with histamine. No abnormal responsiveness to this nonspecific stimulant was noted. For similar reasons, leukocytic transfer sites were repeatedly tested with physiologic and buffered saline, with negative results.

Dilution control tests[1] were performed repeatedly with the serum and plasma of D. G. to rule out the possibility that these media were contaminating the leukocytic preparation in sufficient concentration to produce positive transfer reactions. The results of these tests were uniformly negative.

The possibility that serum reagins might be absorbed or adsorbed by the leukocytes and in this way might be responsible for the positive transfer reactions was investigated in several ways. In early experiments[1] with the leukocytic suspension technique, cells obtained from various donors were washed four times instead of twice. Although this extra manipulation sometimes reduced the size of the transfer reaction, it did not eliminate it except in some instances in which the reactions were doubtful at the outset. When, at a later date, similar experiments were done with D. G. leukocytes and improved techniques were employed, washing the cells four times with the recipient's serum or with Tyrode's solution failed to affect the results of the transfer tests.[2]

In another study, comparisons were made of the transfer properties of D. G. cell preparations which were obtained after shaking periods of variable duration. Leukocytes which had been isolated and washed in the usual manner were shaken (without beads) in Tyrode's solution for two, four, and fifteen hours, respectively (Table IV). Following centrifugation, the supernates and sediments of each cell preparation were used for sensitization of sites on recipients. At the sites prepared with the two- and four-hour preparations, only faint evidences of sensitivity were elicited. Most of the results

consisted of 0± reactions, with only an occasional ± among them. In the two- and four-hour experiments, the average of the transfer reactions was perhaps slightly larger for the residues than for the supernates. After fifteen hours of shaking, however, the supernates yielded sites which produced definite (+) reactions to ragweed, while the results with the residues were negligible (0±).

TABLE IV. TRANSFER TESTS WITH CELL RESIDUES AND SUPERNATES AFTER VARIED PERIODS OF SHAKING

EXPERIMENT NO.	DATE	RECIPIENT	DILUTION	TEST ANTIGEN (MG. N/ML.)	RESULTS OF TRANSFER TEST WITH						
					NORMAL SUSPENSION	2-HOUR		4-HOUR		15-HOUR	
						SUPERNATE	RESIDUE	SUPERNATE	RESIDUE	SUPERNATE	RESIDUE
ES 7	5/1/51	S. W.	1:10	R 0.2	+						
			1:5	R 0.2							0±
				R 0.1						+	
				R 0.2						+	
				T 0.1						0	
				T 0.2						0	
				BS						0	
ES 8	5/23/51	G.	1:10	R 0.1		0					
				R 0.2		0±					
		B. R.	1:10	R 0.1		0±	0±				
				R 0.2		0±	0±				
				R 0.1	0±						
				R 0.2	+						
ES 10	6/13/51	S. T.	1:5	R 0.1				0			
				RSP 0.1				0±			
				RSP 0.2				±			
				TSP 0.1				0			
		G. E.	1:5	R 0.1				0±			
				RSP 0.1				±	±		
				RSP 0.2				0±	0±		
ES 11	6/18/51	W. E.	1:5	RSP 0.1						+	0±
				RSP 0.1						+	0±

R and T = Stock extracts of ragweed and timothy pollens prepared in January, 1951.
SP = Freshly prepared extracts.
BS = Buffered saline.
Sites were prepared with 0.025 ml. of cell suspensions and residues and with 0.05 ml. of supernates.
Sites were tested after seven- to ten-day intervals with 0.02 ml. of antigen.

Additional indications that the transferred substance was an integral property of the leukocyte and not merely an absorbed or adsorbed serum component were provided in another way. Studies were instituted to determine whether it was possible to passively sensitize leukocytes. Cells derived from nonsensitive donors were suspended in the serum of D. G. or in sera with high reaginic titers from other donors clinically sensitive to various types of allergens. After immersion of the cells for one or more days at icebox or room temperatures,* they were used in leukocyte transfer experiments. No definite (at least a ±) positive transfer reaction was ever obtained at sites prepared with such materials.[12]

These findings were in accord with the results of the investigations of Harris and his co-workers,[11] who injected antigen into the pad of the rabbit's

*The intracutaneous injection of incubated cells produced marked inflammation of the sites which precluded their use for transfer tests.

hind foot and then at intervals studied the antibody content of the components of the lymph obtained from the efferent lymphatic of the popliteal node. They found that antibody tended to pass from the lymphocytes into the surrounding lymph but not in the reverse direction. They also demonstrated that viable lymphocytes of normal rabbits, when suspended in fresh homologous lymph fluid of high antibody titer for a period of twenty-four hours at room or refrigerator temperature, did not readily absorb or adsorb antibodies from the fluid surrounding them.

An additional challenge to the concept that leukocyte contamination by serum reagins could account for the transfer phenomenon arose from the fact that the white blood cells of D. G. did not transfer sensitivity to timothy as they did to ragweed. It is significant that no such selectivity was exhibited by this donor's serum reagins in the sensitization of his skin, which responded equally well to tests with both pollens (Table I and Fig. 1). The same held true for the sensitizing power of his serum reagins in the skins of the normal recipients on whom the reagin titrations were done (Table II and Fig. 2). Hence, there is little reason to assume that these serum reagins would selectively sensitize the donor's leukocytes, particularly in the light of the aforementioned experiments in which attempts to passively sensitize human and rabbit leukocytes proved unsuccessful. The available evidence preponderantly supports the conclusion that the mediating principle in the leukocytic transfer phenomenon is a derivative of the cell itself and is not a contaminating serum antibody.

Before leaving the subject of controls, it would not be amiss to point out that, because D. G. served as a donor more than fifty times over an eight-year period and provided more than 350 leukocytic transfer sites, his tests provided unique opportunities for checking the specificity of the reactions obtained. In the early years of the study, the consistently positive leukocytic transfer with ragweed and the equally consistent negative results with timothy became such a regular pattern that any sudden deviation from it attracted attention. The fact that, after four years of positive results with ragweed, the leukocytes of D. G. lost their power to transfer this sensitivity was also significant. Since the experimental methods, materials, technicians, and even some of the recipients had remained the same, it was reasonable to attribute this transition to immunologic changes in the donor. The alterations in his skin reaction, reagin titer, and symptomatology that were devoloping at about the same time supported this interpretation of the findings. Under the circumstances, the consistently negative leukocytic transfer results with ragweed after 1954 served to accentuate, even more decisively than before, the significance of the positive reactions which had been obtained so regularly in the preceding years.

LEUKOCYTIC TRANSFER AND CLINICAL SENSITIVITY

The findings in the case of D. G. do not represent the first or only instance in our experience in which the clinical status of the patient was more ac-

curately reflected by his leukocytic transfer reactions than by his skin test or serum transfer reactions. The first example of this had been noted in the initial report on leukocytic transfer.[1] It concerned an 11-year-old asthmatic boy (V. P.) who exhibited, among other sensitivities, pronounced positive skin reactions and moderate serum reagin titers for ragweed pollen. He showed no symptoms of ragweed hay fever, however, and his leukocytes failed to transfer this sensitivity. Included in that same report were the results of studies on four other patients who were clinically sensitive to ragweed. Positive leukocytic transfers to this pollen were obtained in these patients, although in some cases the skin reactions and reagin titers were no greater than those of Patient V. P.

In another instance,[12] Patient B. K., a young man, showed definite skin reactions to timothy and ragweed pollens but experienced hay fever symptoms only during the grass season. His leukocytes transferred only the timothy sensitivity. In this instance, however, the patient's skin reactions for the grasses were somewhat stronger than those for ragweed. Nevertheless, the case is worthy of note in that it illustrates a positive leukocytic transfer to timothy pollen, a finding never demonstrated with the cells of D. G.

The studies on the relationship of leukocytic transfer to clinical sensitivity will be continued in the hope that they may shed additional light on the factors which determine the "clinical" and "nonclinical" significance of positive skin reactions.

THE SENSITIZING PRINCIPLE

The exact nature of the sensitizing principles involved in the leukocytic transfer experiments on D. G. is still uncertain. The substance bears obvious resemblances to the skin-sensitizing antibody, the atopic reagin. The localization of sensitivity to the injected cutaneous area and the immediate whealing response of these sites to tests with related allergens are among the typical features of reaginic passive transfer phenomena. Some of the peculiarities of the leukocytic transfer reaction, such as size limitation and variability in site response, may rest on technical considerations rather than on the properties of the sensitizing principle. It would, however, be premature to assume at this time that differences do not exist between the atopic reagin as it appears in the serum and the leukocytic transfer antibody. These questions will be discussed at greater length in a future communication.[12]

In D. G. there may have been some relationship between the height of his serum reagin titer for ragweed and the success of the leukocytic transfer tests with this pollen. Such a correlation seemed to apply in other cases as well, but it was by no means a constant finding.[12] Positive leukocytic transfers were obtained in some cases in which the serum reagin titers were comparatively low. Moreover, the failure of D. G.'s leukocytes to transfer timothy sensitivity demonstrated conclusively that serum reagin concentration was not the decisive factor in the leukocytic transfer phenomenon.

MISCELLANEOUS CONSIDERATIONS

The fact that specific treatment with pollen affects the related skin reactions and reagin titers during the first years of therapy and, to a diminishing degree, as treatment continues is well known.[13, 14] There has been no indication, however, that the perennial ragweed therapy, which was started on D. G. in 1945 and predated his leukocytic transfer studies by five years, was influencing the results of the leukocytic transfer tests in his case. Positive leukocytic transfer reactions to various types of allergens have been demonstrated in other donors who have never received any form of hyposensitization treatment.[12]

Because of the importance of the results obtained in the studies on D. G., it may be worth while to consider briefly whether his was a typical example of atopic sensitivity to pollens. To those of us who have had the opportunity of observing this patient throughout most of his life, D. G. presented no unusual immunologic findings if one excepts those brought out in the leukocytic transfer studies. Among the more or less commonly observed features of his pollen history were the fluctuations in his cutaneous reactions to pollens, the changes in his skin reactions conforming roughly to the alterations in his serum reagin titers, the lack of conformity between the cutaneous and reagin findings on the one hand and the patient's symptomatology on the other, the presence of "clinical" and "nonclinical" positive skin reactions to pollens in the same patient, and the conversion of some positive "clinical" reactions to a "nonclinical" state (for example, ragweed) and vice versa (for example, tree pollens). The well-known inadequacies of reaginic data as a guide for the clinical management of pollinosis have again been illustrated in this case. The degree to which the leukocytic transfer results obtained in this donor will be reproducible in other forms of atopy and in other sensitivities with immediate positive skin reactions, including those which are not ordinarily associated with circulating skin-sensitizing antibodies, will be discussed in a future communication.[12]

The failure to demonstrate positive leukocytic transfer reactions in several cases of pollinosis was recently reported by Freedman, Fisher, and Cooke.[15] For the preparation of the leukocytic materials and for the sensitization and testing of transfer sites, they employed techniques that were quite different from those which we have found successful.[2] In the reading and interpretation of the results of their tests, Freedman and his associates state: "Any reaction in which, on visible inspection, there was a wheal obviously larger than the control and in which the area of erythema extended beyond the borders of the wheal was considered to constitute a positive reaction. Any lesser reaction was regarded as inconclusive evidence of a positive transfer." Positive reactions were graded from one-plus (+) to four-plus (++++). With these criteria, it is obvious that these investigators, even with adequate techniques, would have disregarded the small but significant reactions that we obtained in our leukocytic transfer studies.[1, 2]

SUMMARY

In an eight-year study on D. G., an atopic patient with hay fever, an attempt was made to correlate the results of leukocytic transfer tests with his skin reactions, reagin titers, and symptoms. During the early years of observation, while D. G. was having ragweed hay fever and his skin reactions and serum reagin titers for this pollen were pronounced, his reactions to leukocytic transfer tests by both the suspension and the extract techniques were regularly positive. Then as the immunologic status of the patient changed and his skin reactions, reaginic titers, and hay fever symptoms diminished, the leukocytic transfer tests for ragweed became negative. Throughout the major part of this observation period, D. G. showed skin reactions and serum reaginic titers for timothy grass pollen which were as great as or greater than those for ragweed, but his leukocytes never transferred this sensitivity and he never experienced any symptoms attributable to this pollen. Hence, the leukocytic transfer tests more accurately reflected the status of D. G. with respect to his clinical sensitivities to *both* pollens than did his cutaneous tests or reaginic titers.

The transfer principle in the leukocytic preparations bore a close resemblance to the atopic reagin. All findings pointed to the sensitizing substance as a derivative of the leukocytes rather than as a serum component absorbed or adsorbed by these cells.

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ALLERGY TO SNAKE VENOMS

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THERE have been published few cases of allergy to snake venoms confirmed by positive skin tests and the presence of transferable antibodies.

Swinny[5] refers to the case of a patient suffering from brachial neuritis who, after the fifth intramuscular injection of snake venom (species not mentioned), presented an intense local reaction characterized by edema, erythema, and itching. Intradermal injection of the venom gave a positive reaction, and local passive transfer of antibodies was obtained. Mendes[2] reported a case of allergy to bothropic and crotalic venom in a 29-year-old patient with conjunctivitis, allergic rhinitis, and bronchial asthma provoked by inhalation and contact with snake venom used in the preparation of clotting substances. The skin tests presented strongly positive reactions to venoms of the *Bothrops* and *Crotalus* genera. The local passive transfer test was positive for both venoms, and all symptoms disappeared when the patient left the laboratory where the aforementioned clotting substance was prepared. In his work, Mendes discusses the possibility of allergic reactions in subjects sensitized by more than one bite.

Parrish[4] obtained, by means of scratch test and passive transfer of antibodies, positive skin reactions in seven of thirty subjects previously bitten by snakes. Similar tests were negative in twenty control subjects not previously bitten by snakes. Cross-sensitization to the two snake venoms tested was obvious.

Vaughan[6] reports several incomplete observations, mentioning cases of allergy to snake venoms reported by Ray (1934) and Spangler (1931); as there were no bibliographic references, we were unable to secure complete data. Ray's patient had been bitten by a rattlesnake; soon after the second bite three years later, he presented generalized urticaria and shock, followed by exfoliative dermatitis which was more pronounced around the bite. Spangler's observations concern two druggists who developed spasmodic rhinitis and asthma when handling crotalic venom in powdered form.

Some laboratories in Brazil study and prepare clotting substances from snake venom, especially from venom of the *Bothrops* genus. These clotting substances are obtained by heating the venom and processing it physically and chemically; the toxic activity of the venom is considerably decreased without

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any reduction in its clotting capacity. We decided to make an inquiry in three laboratories among workers handling such venoms, and we managed to observe ten persons who were allergic to these substances.

The allergic investigation of six of these cases constitutes the objective of this work.

MATERIAL AND METHODS

Persons working with snake venoms were questioned about allergic symptoms, mainly respiratory and ocular, appearing after contact or inhalation of the above-mentioned allergens.

The investigation undertaken in six of the ten cases with a clinical diagnosis of allergy to snake venom included the following:

1. Allergy questionnaire.
2. Intradermal tests with suspected venoms, using a 0.03 ml. dose in the following dilutions in 0.85 per cent physiologic solution:
   - (a) *Bothrops jararaca*—1 gram in 18,181 ml.
   - (b) *B. atrox*—1 gram in 33,333 ml.
   - (c) *B. jararacussú*—1 gram in 28,571 ml.
   - (d) *B. alternata*—1 gram in 25,000 ml.
   - (e) *B. neuwiedii*—1 gram in 28,571 ml.
   - (f) *Lachesis muta*—1 gram in 25,000 ml.
   - (g) *Crotalus terrificus*—5 minimum lethal doses for the pigeon per milliliter.
   - (h) *Vipera aspis*—$\frac{1}{50}$ minimum lethal dose for the pigeon per milliliter.
   - (i) Coral (*Micrurus coralinus* and *M. frontalis*)—$\frac{1}{50}$ minimum lethal dose for the pigeon per milliliter.
   - (j) Bothropic venoms (three parts) and crotalic (one part) physically and chemically processed for coagulating purposes—1 mg. of powder per milliliter.

   These venoms were also injected intradermally in a group of nonallergic controls to make possible comparison of the readings and to avoid nonspecific reactions.
3. Tests for local passive transfer of antibodies (Prausnitz-Küstner) were carried out in two persons. Control injections of the venoms without previous patient serum injection were always done, as the venoms are considered histamine releasers and may provoke nonspecific reactions.

SUMMARY OF OBSERVATIONS

Case 1.—The patient was R. G., a 26-year-old man. For eighteen months he had been handling snake venoms, weighing and dosing them every eight to 15 days. A year ago he started to suffer from allergic rhinitis followed by conjunctivitis. With more severe attacks he presented wheezing followed by mild dyspnea and cough. He observed that these symptoms

were provoked only by bothropic venom, nothing happening with crotalic venom. Exceptionally, he came in contact with the venom of the *Lachesis* genus.

No personal or hereditary record of allergy was available.

Intracutaneous tests were positive for bothropic venom (++++), crotalic venom (+), and coagulating solution (++). The passive transfer test was positive with all of these venoms.

Case 2.—Patient O. M., a 20-year-old man, had been handling snake venoms for six years. Two years ago he began to show symptoms of allergic rhinitis and conjunctivitis followed by intense itching in the eyes, palate, and pharynx. These symptoms appeared only when he was handling venoms. During the most violent crisis there was wheezing in his chest.

No personal or hereditary record of allergy was available. Intradermal tests were positive for bothropic venom (++++), crotalic venom (++++), and coagulating solution (++).

The passive transfer test was positive with *Bothrops jararaca* (++), *B. alternata* (++), *B. neuwiedii* (++), *Crotalus terrificus* (++), *Lachesis muta* (+), and coagulating solution.

Case 3.—J. S., a 24-year-old man, had been handling venom for eight years. Five years ago he began to suffer from conjunctivitis with itching, allergic rhinitis, cough, and wheezing in his chest. Two months ago he was bitten on the finger by a snake of the *Bothrops* genus and was medicated with 70 ml. of antisnake serum and 1 ml. of epinephrine 1:1,000 intramuscularly. Ten minutes later an enormous edema appeared on his hands, and two hours later his whole forearm and arm were intensely swollen. After another six hours he suffered a violent crisis of asthma and improved only after taking two intramuscular injections of epinephrine 1:1,000.

He did not have any personal record of allergy. Before the accident, he had never received any kind of serum. One of his children has asthma.

Intracutaneous tests were positive for the venom of *Bothrops atrox* and *B. alternata* (+++), *Crotalus* (+++), and *Lachesis muta* (++++), and for coagulating substance (++). The passive transfer test was positive with the above allergens, as follows: *Bothrops atrox* (++), *B. alternata* (+++), *Lachesis* (++++), *Crotalus* (++), and coagulating substance (++).

Case 4.—J. T., a 20-year-old male patient, had been working for five years in all departments concerned with venoms. After two and one-half years of steady contact and inhalation, he started to suffer from conjunctivitis with itching, allergic rhinitis, and asthma. The symptoms appeared when he was in contact with any kind of venom, the bothropic venom being the most active one.

No personal or hereditary record of allergy was available.

Intracutaneous tests were positive for *Bothrops atrox, B. alternata, B. jararacussu,* and *B. neuwiedii* (+++), *Crotalus* (+++), *Lachesis* (++), and coagulating substance (++). The passive transfer test was positive with venoms employed: *Bothrops neuwiedii* and *B. jararacussu* (++++), *Crotalus* (++), *Lachesis* (++), and coagulating substances (++).

Case 5.—L. L. S., a 14-year-old boy, had been handling snake venoms for eight months. Two months ago he began to cough and to experience itching in his nose followed by sneezing when in contact with the venoms in powdered form.

No personal or hereditary record of allergy was available. The intracutaneous tests were positive for *Bothrops jararaca* and *B. atrox* (++++), *Crotalus* (++), and coagulating substance (++). The passive transfer test was positive with these allergens, as follows: *Bothrops jararaca* and *B. atrox* (+++), *Crotalus* (++), and coagulating substance (++).

Case 6.—For a period of four years H. C., a 30-year-old woman, had been working exclusively with venoms of the *Bothrops* genus for scientific purposes. After years of this special kind of work, she began to suffer conjunctivitis, allergic rhinitis, and asthma when in contact with the venom.

No family or personal record of allergy was available.

Intracutaneous tests were not done. Passive transfer tests were positive for all venoms, as follows: *Bothrops alternata* (+++), *B. neuwiedii* (++), *B. jararaca* (++), *Vipera aspis* (+), and coral (+).

RESULTS

Five of the six patients studied were males, and their ages ranged from 14 to 30 years. No patient presented a personal history of allergy, and only one possessed a family history of allergy.

The symptoms appeared after a period of contact with venoms which varied from six months to five years. All patients presented signs of respiratory and ocular allergy. Bothropic venom in powdered form or as vapor was held responsible as the most important agent in all six patients. Patient R. G. (Case 1) reported that he had symptoms only on exposure to bothropic venom. Only two patients were sure of having been in contact with venoms of the *Crotalus* and *Lachesis* genera as well as the *Bothrops* genus. Patient H. C. (Case 6) was studying only venoms of the *Bothrops* genus. No patient reported contact with *Vipera* and coral (*Micrurus*) venoms. Intracutaneous reactions were always unquestionably positive when venoms of the *Bothrops, Crotalus,* and *Lachesis* genera were used, even in patients who had not reported contact with the *Crotalus* and *Lachesis* genera. The same was true of the local passive transfer test, which was positive with the serum of all patients and with the three genera—*Bothrops* with all its species, *Crotalus,* and *Lachesis.*

The serum of the patient in Case 6, who reported contact only with venom of the *Bothrops* genus, presented a positive passive transfer test for three genera (*Bothrops, Lachesis muta,* and a venomous snake nonexistent in our area, *Vipera aspis*).

Patient J. S. (Case 3), developed a typical and violent crisis of asthma six hours after he was bitten by a *Bothrops jararaca.* He had never exhibited such symptoms previously.

DISCUSSION

The allergen contained in snake venoms proved to be extremely potent, as it could sensitize persons with no personal or family record of allergy six months to five years after contact.

It seems to us that there is an allergen, common to all venoms studied, as judged by intracutaneous reactions and passive transfer tests. This fact alone could explain the positive skin reactions to *Lachesis muta* in patients who denied any contact with that venom. The observation made with the serum of the patient in Case 6 was particularly enlightening, for notwithstanding the exclusive contact with venom of the *Bothrops* genus, there were positive passive transfer tests for *Crotalus* and *Lachesis.* This same serum presented positive passive transfer tests with snake venoms of the *Vipera* and coral (*Micrurus*) genera, which are not found in our region or in the patient's laboratory.

Considering each patient separately, the intensity of the skin reactions and of the passive transfer tests was not similar with the various venoms. This probably suggests that, besides the common allergen responsible for the cross-reactions, there could be antigens peculiar for each of the venoms.

It is interesting to observe that although the venoms used for therapeutic purposes undergo a "detoxicating" process by means of heating and chemical agents, they do not lose their allergenic capacity.

Future research, using other immunologic methods, could definitely shed light on this question, just as the studies reported by Loveless and Fackler[3] and Foubert and Stier[1] recently demonstrated the occurrence of immunologic cross-reactions among the various bee venoms.

Another aspect which merits discussion is the possibility of sensitization to venom in subjects who are bitten by snakes. Under these conditions, a second bite could provoke, in addition to the toxic symptoms, an outbreak of symptoms of an allergic nature. The patient in Case 3, six hours after being bitten by a snake of the *Bothrops* genus, suffered a violent crisis of asthma, whereas one of his colleagues, who was not allergic to the venom, was bitten on the same occasion by a similar snake and presented only toxic symptoms. The possibility of such symptoms being due to horse serum was practically eliminated, since the patient had not received injections of serum in the past. However, the patient's sensitivity to horse serum was not tested.

Parrish[4] acknowledges the possibility of fatal anaphylactic reactions when previously sensitized persons are bitten again.

We are prone to believe that more accurate allergy research in patients repeatedly bitten by snakes could produce more enlightening and interesting contributions concerning the immunopathology of venoms.

SUMMARY

1. Six cases of allergic reactions to inhalation of snake venom, characterized by ocular and respiratory symptoms (conjunctivitis, rhinitis, and asthma), have been studied.

2. The patients worked mainly with venoms of the *Bothrops* and *Crotalus* genera, in powdered or vapor form, and the outbreak of symptoms occurred from six months to five years after the contact.

3. The presence of skin-sensitizing antibodies was demonstrated by means of unquestionably positive intradermal reactions and passive transfer tests.

4. It seems that there is a common allergen to all venoms studied (*Bothrops, Crotalus, Lachesis, Vipera* and *Micrurus*), since some patients presented positive reactions to intracutaneous or passive transfer tests with venoms with which they had not had any previous contact.

5. Snake venom allergens seem to be extremely potent, inasmuch as five of the six patients studied did not present any personal or family record of allergy.

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DOES THE ALLERGIC DIATHESIS INFLUENCE MALIGNANCY?

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CANCER and the clinical course that it pursues can no longer be regarded as resulting only from ungoverned growth of malignant cells in a passive, nonresisting host. Rather, various studies suggest that natural defenses against cancer exist. These may explain the differences between a cancer-prone and a cancer-resistant person and differences in the rate of tumor growth, invasiveness, curability, and, on very rare occasions, spontaneous disappearance of the malignancy.[1]

BACKGROUND MATERIAL

Rhodenburg,[2] as early as 1918, and more recently Everson and Cole,[3] in 1956, concluded that spontaneous regression of tumors occurred in nearly all types and varieties of malignancy. Other investigators, such as Black and associates,[4] have emphasized the variability of the indivdual course of the malignant process and concluded that autonomy of growth is only one of several forces determining the course of the disease. A recent report from the Mayo Clinic by Pawlias, Dockerty, and Ellis[5] indicates that in patients with late recurrences of cancer of the breast, the local recurrences and distant metastases had remained dormant for long and variable periods of time. They attributed this phenomenon of variable dormancy to individual host resistance. Interestingly, once host resistance was overcome, the subsequent clinical course and survival in all the patients was similar (two years).

In our series the not infrequent occurrence of multiple simultaneous primary malignancies or development of a new primary malignancy at a subsequent date suggests lack of resistance to neoplasia on the part of the host (Table III).

Frank's[6] postmortem studies contribute further evidence in support of the host's role in resistance to cancer. He showed a significant incidence of latent cancer of the prostate, lung, kidney, and, to a lesser degree, of the thyroid and stomach.

Genetic and immunologic factors which limit transplantability of malignant tumors to new hosts were outlined by Strong[7] as early as 1926. In contrast with the preceding definite picture, however, Schultz[8] recently drew attention to "experiments in which tolerance is induced, or histocompatibility barriers are overridden, or tumors are enhanced in their growth or adapted

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to their hosts.'' In a discussion of the immunology of cancer, Green[9] has recently stated that the loss of ''self-markers'' of cancerous cells represents the central feature in the development of malignancy.

The experiments of Mider and associates,[10] as well as others, show that in the early stages of cancer the serum globulin and serum fibrinogen levels of many patients are elevated and are comparable to elevations noted in infection. Graham and Graham[11, 12] demonstrated the presence of antibodies in some patients during the early stages of cancer and the disappearance of antibodies in the late stages. They report that patients with cancer of the cervix with a good prognosis have circulating antibodies, but other patients with a poor prognosis have none.

It has been established, in experiments conducted at the Sloan-Kettering Institute,[1] that it is possible to immunize human beings against transplanted tumors but not against their own cancers. Cancer has also been successfully transplanted to volunteers who were already suffering from cancer but not to noncancerous patients. A further study conducted at the Ohio State Penitentiary suggested that a normal person may develop not only immunity to a single transplanted tumor but, simultaneously, cross resistance to other types of human tumors. In recent studies a lipid antigen, cytolipin-H, has been isolated from over twenty different specimens of human cancer; this antigen, which is now available in pure form, occurs in only one normal tissue, the spleen, although in much lower concentration, and might form the basis for a simple immunologic test for cancer.[1]

Strauss, Saphir, and Appel[13] found in over 350 patients that necrotic tumor tissue (the result of incomplete coagulation of tumor of the bowel) produced disappearance not only of the tumor but, in many of the cases, of distance metastases as well. The results equalled those obtained by surgery. The authors concluded that necrotic, coagulated tissue in situ served as an antigen, eliciting an antibody response that resulted in destruction and reabsorption of the residual tumor.

Interestingly, levels of properdin are markedly depressed in cancer but unaffected in leukemia.[14-19]

These background data indicated that host resistance is important and suggested that tumor tissue, if sufficiently differentiated from the host's normal tissue, might induce the formation of cytotoxic autoantibodies in some persons.

Thus, if the cancer cell represents an antigen, it seemed worth while to study the incidence and progress of malignancies in a group of patients who are distinguished by a single immunologic characteristic, atopy. The atopic state is characterized by an excessive immune response to substances that are nonantigenic to the nonatopic population.

EXPERIMENTAL PROCEDURE

Criteria for Atopy.—The patients were interviewed at random as they presented themselves to the various clinics. Only patients with clear mental

states were included. None of the cancer cases were terminal. The criteria for atopy were rigid in order to rule out nonatopic disease with similar symptoms (for example, infectious bronchial asthma and primary pulmonary emphysema). Atopy was assumed to exist in the presence of a history of seasonal rhinitis or bronchial asthma, even though the respiratory symptoms had become perennial during the course of the years. Atopic flexural eczema was also classified an atopic state. Classification was based essentially on the history, but half of the patients were tested to seasonal air-borne antigens and to house dust in order to verify the classification. Patients who were clearly atopic but had negative skin tests were rated questionable but statistically were included as positive atopic patients.

Criteria for Malignancy.—Tumors were classified according to type and severity (1+ to 4+). In this type of grading, 1+ represents a low-grade malignancy; 2+, a malignancy without a known metastasis; 3+, a malignancy with local spread; and 4+, a malignancy with widespread metastases.

TABLE I

TUMORS	NUMBER	ATOPY	(?)ATOPY	PER CENT ATOPY
Lungs	48	0	1	2.1
Uterus (gynecologic)	347	6	2	2.6
Breast	192	4	1	2.6
Genitourinary	105	2	1	2.8
Miscellaneous	179	5	1	3.3
Gastrointestinal	145	4	1	3.4
Skin	131	5	0	3.8
Ovary	38	4	1	13.1
Total	1,185	30	+ 8 = 38	= 3.2

RESULTS

Our study to date includes 1,185 patients with malignancy and 294 patients without malignancy in comparable age control groups (Table I). The incidence of atopy in patients with malignant tumors was thirty-eight out of 1,185 patients, or 3.2 per cent. This is significantly below the expected average in the normal population, which is approximately 10 per cent. In the control group of noncancerous patients we found an incidence of 12.9 per cent of atopy; this difference is significant. Of the thirty-eight patients

TABLE II

CONTROLS	NUMBER	ATOPY	PER CENT ATOPY
Genitourinary clinic	18	3	0
Benign tumor	20	2	1
Orthopedic clinic	134	15	0
Orthopedic ward (female)	40	6	1
Orthopedic ward (male)	54	5	1
Benign condition, radiology clinic	28	3	1
Total	294	34	+ 4 = 38 = 12.9%

Statistical evaluation, Tables I and II ($p<0.001$).

in the cancer group, fourteen reported a complete remission of allergic symptoms ten or more years prior to the interview; two noted a remission of atopic symptoms about the time that the diagnosis of cancer was made. Only one of the thirty-eight patients had severe atopic disease.

TABLE III

NO. OF CANCER PATIENTS	NO. WITH MULTIPLE PRIMARY MALIGNANCIES	PER CENT
1,185	21	1.7

SUMMARY

1. Atopic disease occurs in patients with malignant tumors.

2. The incidence of atopic disease in patients who suffer from malignancy appears to be significantly below the incidence of atopic disease in control groups of noncancerous patients and in the general population.

3. In fourteen of thirty-eight atopic patients with cancer, atopic symptoms disappeared at least ten years prior to the recognition of the malignancy.

4. The largest group of tumor patients, those who suffer from cancer of the uterus, prostate, and breast, show a particularly impressive decrease in the incidence of atopy.

5. Ovarian cancer to date represents the one exception to the pattern which we have found.

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AMERICAN ACADEMY OF ALLERGY

REPORT OF THE RESEARCH COUNCIL, AMERICAN ACADEMY OF ALLERGY, 1958-1959

THIS report is divided into two sections—(1) reports of the individual committees and subcommittees and (2) a report on general and administrative matters pertaining to the Research Council as a whole. It is to be noted that because the new policy of inviting Academy members to apply for membership on the Research Council became effective after the 1958 meeting of the Academy, the many new committee members have never had an opportunity to meet with their respective committees. It is anticipated that these new members will be able to contribute more effectively to the work of the Council after they have met with their committees in February, 1959.

I. COMMITTEE REPORTS

A. *Committee on Aeroallergens (Dr. Lawrence J. Halpin, Secretary).*—

(1) *Subcommittee on Pollen and Molds.* This group again has conducted its annual extensive survey of pollen and mold counts in many areas of the United States, Canada, Mexico, and foreign countries. Results of the survey again have been presented in the form of a scientific exhibit at the Academy meeting, and the exhibit also has contained some new features, including information about ragweed control measures in Oregon. The prolific correspondence of the Committee has indicated increased interest in pollen research, particularly on the part of state and city departments of health.

Several special regional aerobiologic studies have been inaugurated in which the Committee secretary has served as consultant or director. These include studies in the San Fernando and Napa Valleys of California and in the Virgin Islands National Park and the adjacent parts of St. John Island. A comprehensive air-sampling program in the San Francisco Bay area and adjacent centers of population is being established by the Allergy Foundation of Northern California and the California State Board of Health.

A Committee member, Dr. Eugene C. Ogden, has consulted with other members of the Committee in setting up an extensive two-year study of basic problems of pollen dispersal and accurate volumetric sampling at the Brookhaven National Institute. The possibility of using tagged ragweed pollen grains in such studies is being evaluated.

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The Oregon State Department of Public Health, the Oregon State Department of Agriculture, and the Portland newspapers have been given hearty support and commendation by the Committee for efforts to prevent the spread of ragweed in western Oregon, an area in which control measures give reasonable promise of success.

During 1958 the Herbarium sent 272 pollen specimens in response to ten requests. The Herbarium also has sent a questionnaire to all those who have requested pollen slides in the past two years. This is an effort to see if the service of the Herbarium can be improved.

Membership: Oren C. Durham, secretary for pollen; Dr. David Merksamer, secretary for molds; Dr. Ralph Voigt, curator of the Herbarium; Drs. Bernard T. Fein, Lowell Henderson, Eloise Kailin, Eugene C. Ogden, George A. Peck, Frank Perlman, Merle S. Scherr, Bernard B. Siegel, Jay Spiegelman, Abram M. Targow, and Matthew Walzer.

2. *Subcommittee on Insects:* This subcommittee, together with the Insect Allergy Study Group, met on Feb. 2, 1958, with twenty-three persons in attendance. The secretary reported on his activities in the field of insects as inhalant allergens, on the material received and distributed upon request, and on the results of the questionnaires sent out to the members of the group regarding their clinical experiences in this field. The major portion of the meeting was devoted to a discussion of allergic reactions to bites and stings of insects with special emphasis on the *Hymenoptera.* Many of those present participated in this active and informative discussion.

Activities of the subcommittee during the year have centered around the following:

(a) Insect material was received, prepared into allergenic extracts, and redistributed to persons providing data to the Committee.

(b) Insect allergens on hand were supplied upon specific requests of persons providing data to the Committee.

(c) Miscellaneous services given included photographing materials, replies to inquiries, and identification of insect specimens.

Membership: Dr. Frank Perlman, secretary; Drs. Richard L. Etter, Alan R. Feinberg, Harry L. Mueller, and Willard S. Small. Insect Allergy Study Group: Drs. James H. Barnard, I. Leonard Bernstein, Norman Cohen, Claude A. Frazier, Sidney Friedlaender, Frank Furstenberg, Max Grolnick, Emanuel Hellreich, Gustavus A. Peters, Merle Scherr, Joel D. Tiegland, and Paul Winer.

3. *Subcommittee on Weather:* Twelve persons attended the meeting of this subcommittee in February, 1958. In discussing the group's major project of trying to make correlations between symptoms of asthmatic patients and changes in the weather, it was the unanimous opinion that attention should be focused on one month of the year, possibly November. It also was deemed advisable to have patients report their symptoms by postcard at relatively frequent

intervals. No attempt will be made at selecting particular types of asthmatic patients for the present.

The projected study was carried out in November, 1958. In some localities there were so few instances of simultaneous attacks of asthma among the patients studied that the data were not of much value, but in three places (Pittsburgh, Iowa City, and Palo Alto) there were enough coincidental attacks of asthma that a more detailed analysis of the data in relationship to meteorological factors is being carried out.

Membership: Dr. Harold S. Tuft, secretary; Drs. John Beakey, I. Leonard Bernstein, Van Vleck Chambers, Armand Cohen, Norman Cohen, Frank F. Furstenberg, Daniel H. Goodman, Lowell Henderson, Macy I. Levine, Frank Perlman, Paul M. Seebohm, Edward E. P. Seidmon, and Paul VanArsdel, Jr.

4. *Subcommittee on Air Processing:* During 1958 this subcommittee has investigated one filtering device submitted by its manufacturer through the facilities of the Farr Company of Los Angeles. A number of inquiries regarding filtering devices have been answered. An exhibit by this subcommittee was arranged for the annual meeting of the Academy under the chairmanship of Dr. Harry Huber. Testing selected additional air-filtering devices at Research Council Expense has been recommended.

Membership: Dr. Willard S. Small, secretary; Drs. Harry Huber and Frank Simon.

B. *Committee on Contactants.*—Five members of this committee met on Feb. 1, 1958. Following a discussion of possible courses of action, the following activities and duties of the Committee were formulated: (1) registering of new contact allergens and their test concentrations with the Committee secretary; (2) members of the Committee and others, if they so choose, may list with the secretary research studies which would seem to be of interest to the Committee; (3) a closer relationship with the Food and Drug Administration is to be encouraged.

Considerable information concerning contactants of recent interest was collected by the Committee, and this material is being published as a separate report.

Membership: Dr. Max Grolnick, secretary; Drs. Rudolf L. Baer, Donald J. Birmingham, George H. Curtis, Merrill W. Chase, Naomi M. Kanof, John L. Fromer, Irvin Kerlan, Morris Leider, Rudolf Mayer, Samuel M. Peck, Marion B. Sulzberger, and Raymond R. Suskind.

C. *Committee on Drugs.*—In addition to its usual advisory services to allergists and governmental agencies, the Committee has evaluated three agents in the past year. The results of these studies were presented at the annual meeting of the Academy and are being published in the JOURNAL OF ALLERGY.

Membership: Dr. Sidney Friedlaender, secretary; Drs. Murray M. Albert, Theodore B. Bernstein, Robert J. Becker, Earl B. Brown, Monroe Coleman,

Seymour Crepea, Edmund E. Ehrlich, Alex S. Friedlaender, Henry T. Friedman, Joseph B. Fries, Harold J. Friedman, Claude A. Frazier, Frank T. Joyce, Samuel J. Levin, Walter R. MacLaren, Lloyd Mayer, Dean Moffat, Milton Mosko, George Peck, Gustavus Peters, Simon Rubin, Norman P. Richard, Samuel E. Rynes, Burt B. Schoenkerman, Sheppard Siegal, Aaron Speilman, Irving Schiller, Isadore Pitesky, and Paul VanArsdel, Jr.

D. *Committee on Food Allergy.*—In collaboration with the Committee, Dr. Sheldon Cohen has completed some very interesting serologic studies pertaining to the antigenic interrelationships between members of the crustacea family. He also has carried out studies on the presence of fish antigen in various commercial fish products and fish odors. This work was presented on the regular Academy program.

Two other projects have been outlined in detail after consultation between the Committee secretary and various Committee members. One is concerned with the effect of various extracting procedures on the allergenicity of the resultant extract, and the other relates to the rate of deterioration of allergenic extracts. The two projects could be run simultaneously with the same sera and the same set of allergenic extracts. However, more reaginic sera are required in order to carry out these experiments.

Membership: Dr. George I. Blumstein, secretary; Katherine Bowman, Drs. Sheldon Cohen, George Frauenberger, Henry T. Friedman, Joseph H. Fries, Eloise W. Kailin, Morris Kaplan, Saul Malkiel, Lloyd D. Mayer, Bernard Siegel, Margaret Strauss Ballard, Abram Targow, and Richard Wiseman.

E. *Committee on the Reagin Bank.*—The Reaginic Serum Bank has continued to collect, process, store, and send out sera. Some of these sera are being used by the Committee on Food Allergy. There has been a special demand for sera containing reagins to penicillin.

Membership: Dr. Bernard B. Siegel, secretary, Katherine Bowman, Drs. Sheldon G. Cohen, Harold J. Friedman, Morris Kaplan, and Jerome Sherman.

The following persons accepted appointments to the Advisory Board to the Research Council: Samuel M. Feinberg, M.D., Harry Hayes, Ph.D., Alfred Gilman, Ph.D., Irvin Kerlan, M.D., William Sherman, M.D., Matthew Walzer, M.D., and Charles Woodworth, Ph.D.

II. GENERAL AND ADMINISTRATIVE REPORT

In accordance with changes in the rules of the Research Council approved by the Governing Board in February, 1958, members of the Academy were invited to apply for membership on the Research Council at the annual business meeting of the Academy and by written notice published in the Academy's "News and Notes." Previous members of the Council also were required to submit applications if they wished to maintain membership. This new procedure has effected a major turnover in Research Council personnel. Of the 119

appointments made in 1958, 45 per cent were new appointments and 55 per cent were reappointments, the total membership on the Council remaining about the same.

The secretary of the Research Council consulted with the chairman of the Committee on Constitution and By-Laws regarding proposed changes in the Academy By-Laws pertaining to the Research Council along lines requested by the Academy's Executive Committee. These changes subsequently were put into effect by vote of the Academy at its annual business meeting in February, 1959.

At the meeting of the Governing Board of the Research Council on Feb. 6, 1959, the Committee on Aeroallergens was abolished, since it was carrying out no functions per se and some activities of its subcommittees were not related to aeroallergens. The previous subcommittees of the Committee on Aeroallergens were made full committees of the Research Council, the committee secretaries thereby becoming voting members of the Governing Board. These are the Committees on Pollen and Mold, Insect Allergens, Weather, and Air Processing. The subcommittees on the Committee on Contactants were abolished. The Reaginic Bank requested that the Executive Committee obtain legal opinion concerning the liability of the Academy, Research Council, and operators of the Reaginic Bank for any ill effects of sera provided by the Reaginic Bank.

The Governing Board gave further consideration to means of encouraging promising undergraduate medical students to enter careers as investigators in fields relating to allergy. It again was recommended to the Academy's Executive Committee that the Academy offer some type of award to undergraduate medical student(s) for excellence in research in allergy.

From Washington it was noted that two specific questions about allergy are being included in the National Health Survey questionnaire. Much information concerning current research in the field is available through the Bio Sciences Information Exchange. The F.D.A. is interested in problems arising from the presence of antibiotic residues in milk, poultry, and deodorants. Abolishing the Subcommittee on Legislation of the Committee on Contactants leaves the Academy with no Committee on Legislation. This will be called to the attention of the Executive Committee. The Governing Board does not feel that such a committee belongs in the Research Council.

The status of the Herbarium was reviewed by Ralph Voigt, curator. Although there are some evidences of dwindling interest in this activity, it was felt that the Academy membership would have much interest in newer aspects of botany pertaining to allergy.

Since the Academy receives many inquiries about air-filtration devices, and since several of the available types have never been tested by the Air Processing Committee, it was recommended to the Executive Committee that selected filters be tested at Academy expense.

Allergists have a stake in the expanding programs for studying air pollution. Consideration is being given to the possible future development of a Research Council Committee on Air Pollution or expansion of the activities of the Committee on Weather to include work in this field.

Dr. Sheldon Cohen was elected to succeed Dr. George I. Blumstein as secretary of the Committee on Food Allergy. The Council expresses its appreciation to Dr. Blumstein for his many years of work on the Council.

Respectfully submitted,

Kenneth P. Mathews, M.D.
Secretary

REPORT OF THE COMMITTEE ON CONTACTANTS AMERICAN ACADEMY OF ALLERGY

THE Committee on Contactants has been engaged in several "stand-by" activities.

I. REGISTERING OF NEW CONTACTANTS

(A) Dr. Donald J. Birmingham reported on epoxy resins and their diamine or triamine catalysts. The following is a direct quotation from a letter from him:

We have visited several plants in which epoxy resins and their amine catalysts were being handled. Dermatitis was and continues to be a common accompaniment in the handling of these chemicals. In our laboratory, two epoxy resins, one of low molecular weight and one of high molecular weight, along with two amine hardening agents, were studied for cutaneous primary irritation and sensitization. Irritation studies were conducted on white male rabbits. We found the low-molecular-weight epoxy resin to be an irritant in concentrations at about 30 per cent, whereas the high-molecular-weight epoxy resin produced no irritation. One hardening agent (metaphenylenediamine) was an irritant at about 15 per cent; the other hardener (diethylenetriamine) was an irritant at 0.5 per cent. Intradermal sensitization routines using the materials were conducted on guinea pigs. The low-molecular-weight epoxy and the diethylenetriamine successfully sensitized the guinea pigs. The high-molecular-weight epoxy did not sensitize the guinea pigs; nor did the metaphenylenediamine hardener. This work bears up what has been seen in the field.

Dr. Birmingham also adds the following comments regarding Thermo-Fax paper:

The cases of contact dermatitis due to Thermo-Fax paper were believed to be based on specific sensitization to tertiary butyl catechol contained within the paper. Several such cases were seen and reported upon; however, the company which manufactures this paper has apparently altered it in such a way that dermatitis is no longer occurring among the handlers.

(B) Dr. George H. Curtis wrote concerning his experiences with zirconium:

In regard to zirconium, we have had four cases of the pure contact dermatitis of the eczematous type. These were not complicated by the granuloma. Positive patch tests were obtained in aqueous solutions of concentrations of sodium zirconium lactate, as low as 5 per cent. Controls with concentrations up to 50 per cent were negative. We also tested these patients with zirconium hydroxide and oxide (ingredients in poison ivy lotions) with negative results. I believe these insoluble salts are inert in so far as contact dermatitis is concerned. The source of the sodium zirconium lactate had been in the stick deodorants. I believe the manufacturers of these deodorants have eliminated the soluble zirconium salts from the deodorants.

Received for publication June 10, 1959.

(C) Dr. Marion B. Sulzberger, through Dr. Norman Kanof in charge of the Allergy Section of the Skin and Cancer Unit of New York University, supplied the following list of materials for patch testing:

MATERIALS AND SOURCE	TEST CONCENTRATION
2, Amino, 5 diethylaminotoluene (CD_2) (color photo developer)	2 per cent in petrolatum
Monobenzylparaaminophenol (BD80) (color photo processing)	2 per cent in petrolatum
Thermo-Fax paper (active ingredient—tertiary butyl catechol)	As is
Thiobetanaphthol (rubber, rubber cement, shoes)	3 per cent in petrolatum
Bis (dimethyl thiobenzyl) disulfide (tetramethyl thiuram-disulfide) (rubber, rubber cement, shoes, soap)	1 per cent in petrolatum

(D) Dr. Rudolf L. Baer, with Dr. Victor H. Witten as coauthor of the 1957-58 volume of the *Yearbook of Dermatology and Syphilology* presents a lead article entitled "Allergic Eczematous Contact Dermatitis" and an up-to-date list of substances, concentrations, and vehicles for use in patch testing.

II. REGISTERING OF RESEARCH STUDIES

All but three of the Committee members are engaged in research studies on subjects related to the interests of this Committee. Of special interest is the continued study by Dr. Merrill W. Chase on the genetic improvement of guinea pig stocks to enhance the testing of contactants.

III. RELATIONSHIP WITH THE FOOD AND DRUG ADMINISTRATION

Dr. Irvin Kerlan stated that he was to present an exhibit entitled "Medicine Advances With Safe New Drugs" at the forthcoming meeting of the Academy. He is, moreover, in the process of compiling a list of new sensitizing agents (contactants) and will offer this at a later date. He recently submitted several releases from the F.D.A. on the dangers of using Ten-Day Press-On Nail Polish. This product was removed from the marked by action of the F.D.A.

Dr. Adolf Rostenberg, Jr., made the following comments concerning his study of this problem in a letter to me:

> My studies with the Ten-Day Press-On Nail Polish consisted merely of observing women who were wearing the nails plus various buffer coats which the manufacturer hoped would prevent damage. Unfortunately, these did not do so, although some of them slowed up the rate at which damage would develop. In no case was the damage really serious. The damage consists of a flaking of the nail plate and of the ultimate development of horizontal cracks, so that the nail breaks off at the proximal portion of the free edge. I am reasonably convinced this arises because of physical alterations, such as trauma incident to the removal of the nails and most likely the incorporation of the adhesive material into the nail plate so that it loosens the lamella thereof and makes it more friable. I am certain that there is no sensitization. I observed several hundred women for almost a year and saw no evidence whatsoever to indicate that any had become sensitized.

Through Dr. Harold Jacobziner, assistant commissioner of the New York City Department of Health, I learned of hazards from the handling of toys and novelties imported from Haiti:

> The United States Public Health Service recently warned that Haitian voodoo dolls used as novelties and "swizzle sticks" can be harmful to persons who handle them. The cashew-nut "heads" of these dolls contain a shell liquid which is similar to the oil of poison ivy. Some volunteers of the Public Health Service who were tested with pieces of the shell developed blistering skin reactions resembling poison ivy within 35 to 50 minutes. An allergic outbreak was also reported involving 50 students in a high school in Atlanta, Georgia. The eyes of these dolls are even more dangerous than the cashew-nut heads; the eyes are believed to be lethal jequirity beans. According to the United States Public Health Service, animal tests indicate that one of the "eyes," when ingested or swallowed by a young child, can cause serious illness which may possibly terminate fatally.

For those who wish to explore this problem further, an epidemic of poison-ivy-like contact dermatitis due to the handling of toys made from cashew nuts (*Anacardium occidentale*) imported from Puerto Rico has been reported by L. Orris in an article entitled "Cashew Nut Dermatitis" (*New York J. Med.* **58**: 2799, 1958).

MISCELLANEOUS INFORMATION

In answer to a question directed to him concerning the preferred method of treatment of ragweed-oil dermatitis, Dr. John L. Fromer states that he favors the injection method of "hyposensitization."

Dr. Samuel M. Peck calls attention to the role of urea-formaldehyde resin as the sensitizing agent in "wet-strength" facial tissues.

For those who are interested in the activities of the Committee on Toxicology of the American Medical Association, the following two articles by Dr. Bernard E. Conley, its secretary, are suggested for reading: Toxicity Problems of Cosmetics, J. A. M. A. **166**: 638, Feb. 8, 1958; and Principles for Precautionary Labelling of Hazardous Chemicals, J. A. M. A. **166**: 2154, April 26, 1958.

In terminating this report, I would like to state that the present structure and functions of the Committee on Contactants can be useful to the Academy in a "stand-by" or "watchdog" capacity. It should be possible in the future to submit an interim report. I hope that this report will be made available to the membership, and that the information contained therein will be of help to some of them.

Respectfully submitted.

Sincerely yours,

Max Grolnick, M.D.
Secretary, Committee on Contactants

ON THE IMPOSSIBLE

Max Samter, M.D., Chicago, Ill.

THE year of the president is a short year. The annual meeting is the year's goal and fulfillment. The crowded tables of the postgraduate course, the inventory of allergy at a scientific session, the ever-larger exhibits, the subdued excitement of research in progress, the reunions of friends, debate and acclaim, argument and resolution make up the old familiar pattern of each late winter or early spring. It must make every president humble to recount at the end of his term the devotion of the members who have served with him—in office, on committees, as individual counselors. Tomorrow's business meeting will bring you the reports of what we have done and where we have gone. It is the president's privilege to talk to you today about what the year of the presidency has meant to him.

A significant part of the president's year—and a significant part, I believe, of the year of many of our members—was spent in Europe. The year 1958 was the year of the Third International Congress of Allergology, held in Paris and competently and elegantly organized by Dr. B. N. Halpern and his tireless staff. The reception in the magnificent semidarkness of the Louvre, the lecture halls of the new Faculty of Medicine, Professor Portier's address which recalled the discovery of anaphylaxis, and the evenings at home with Sir Henry Dale holding court and seminar in Dr. Halpern's living room, the outings, and the festive gathering at the opera are memories which will remain with us for many years.

Allergy in Europe differs from allergy in the United States. The atmosphere of a congress—its brilliant lights, its restless activities—tends to obscure the difference. I got an inkling of it even there, however, when I attended, by invitation, a meeting of the German East-West Research Council on Allergy. It became unmistakable after I left France and visited some of the workshops of allergy on the Continent—Jamar in Brussels, Benos in Athens, Letterer in his quiet room at the top of a hill which overlooks the town of Tübingen, Herxheimer at the Rudolph Virchow Krankenhaus in West Berlin, Findeisen at his outpost in the eastern sector. The setting differs; allergists in Europe have just begun to organize and do not enjoy the strong representation and the solid organizational framework that we have known since the days of early amalgamation. They rely on their own resources; their strength is the strength

Presented at the President's Luncheon, fifteenth annual meeting of the American Academy of Allergy, February, 1959.

of the pioneer. In some sectors of Europe allergists struggle with apathy and indifference; other parts show early indices of growth and consolidation. Benes, my host in Athens, has left the silence of the laboratories for the missionary work that remains to be done in Greece, as elsewhere. He does not complain; he is a man with a plan and a purpose. So are the others: Herxheimer, who has brought the tools for objective evaluation of bronchial asthma across the Channel; Letterer, who has succeeded the late Robert Rössle as the leading pathologist of European allergy; and Findeisen, who is trying to bridge the gap which separates East and West.

How fortunate we are, one thinks, that we are not alone. One thousand of us share the same experience, the same concern. We are strangely fortified by comprehending that, unlike the European allergists who, as it were,

Professor Portier (with B. N. Halpern), patron saint of the Third International Congress of Allergology, as he accepts the standing ovation of the assembly.

live in the Diaspora, we are part of a unit which is dedicated to "the advancement of knowledge and practice of allergy, by discussion at meetings, by fostering the education of students and the public, by encouraging union and cooperation among those engaged in this field, and by promoting and stimulating research and study." It is the aim of these brief remarks to examine the state of allergy, the state of the community of allergists to which we belong, and finally the state of the world which surrounds us.

The constitution of the American Academy of Allergy, which I have just quoted, considers allergy, at least by implication, a uniform and manageable concept, more so, a concept that could be taught, with promise, not only to

ourselves, but to our friends and patients. Why, then, in presidential remarks of recent years the growing impatience; the growing emphasis on our inadequacies rather than on our accomplishments; the growing search, so eloquently stated by Carl Arbesman, for new and different approaches? Allergy has outgrown its adolescence; innocence and the paradise have been lost. For each phase of allergy, the antigen, the antibody, the chemical mediators, the tissues in which antigen-antibody union occurs, and new and refined techniques have been designed and have rendered not only old techniques but also old conclusions obsolete. As in medicine at large, progress in allergy has become progress in instrumentation, in adaptation of physics and chemistry to our particular needs. How far we have traveled was brought very close to me this morning when a reporter approached, program in hand, after Talmage's discussion of the use of isotopes in experimental allergy. "Would you, in words which our readers can understand," said the reporter, "enlighten me on the difference between 'hot' and 'cold' antibodies?"

Investigative techniques are now so specialized that modern man of science, like modern man, has come to depend on the intricate services of so many others that he has developed a deep affection for the simplicity of the Middle Ages and of the Renaissance, in which man could still afford to be universal. Such nostalgia is, indeed, understandable, and I was deeply moved by Sir Henry Dale's* remarks on the progress of allergy since the discovery of anaphylaxis by Portier and Richet.

> Now this subject spread in all directions through the recognition of the fundamental analogy between the experimental anaphylaxis in animal and the natural allergies in man. And to some of us whose memories go back a long way and who are able to see the subject in its early stage in what was perhaps a misleading simplicity, it seems now that the broad outlines of the subject or certain parts of them are now in some danger of becoming blurred by the appearance of an ever increasing complication of details and discrepancies.
>
> I feel confident, however, that simplification will come again and reveal the main outlines with a more correct shape and perspective though I am equally sure that the subject will not be exhausted and that with a clearer understanding even more successful methods of relieving the human sufferings caused by allergy in its different forms will eventually be found.

Progress in experimental allergy has gone beyond our most hopeful imagination; there is little reason to believe that its pace will slacken or that we will be allowed to return to a simpler past.

Clinical allergy, on the other hand, has moved in a different direction. Its scope has widened. In a recent letter Dr. A. McGehee Harvey, chairman of the Department of Medicine, Johns Hopkins Hospital, has outlined some of its new horizons:

> Allergy is a unique field in medicine because it deals with a mechanism of disease rather than a specific disease or group of diseases. Although the allergist has in the past, and at present, dealt largely with asthma, hay fever and urticaria, it has been necessary to incorporate in his thinking seemingly unrelated diseases, such as agammaglobulinemia, Hashimoto's thyroid struma, acute acquired hemolytic anemia, transfusion reactions, homo-

*From *Le courrier du congrès* (Third International Congress of Allergology), fourth issue, October, 1958.

transplantation, etc. This has been necessary for the simple reason that the same underlying mechanism of host injury (antigen-antibody) is involved. This diversification of the allergist's interest has been valuable for it necessitates his becoming aware of the real nature of his clinical activity and research. For allergy to continue to grow as a scientific medical discipline, a greater awareness of the broad ramifications of the mechanism of disease which it studies will be required. The allergist will no longer be able to restrict his attention exclusively to asthma, hay fever, and allergic skin disease, even though patients with these illnesses will continue to compose the bulk of his practice in allergy.

Designs for a comprehensive training program recognize that allergists must be familiar with immune mechanisms which we are just beginning to understand and with the tissues in which they occur. In addition, however, they must be trained in an extraordinary spectrum of medical competence. I cannot think of any specialty which requires those who practice it to be internists, pediatricians, endocrinologists, psychiatrists, dermatologists, and otolaryngologists. One of our European friends summarized our predicament rather neatly when he wrote:

> It is impossible to predict the outcome of studies which will explain the nature and localization of immune mechanisms in tissues. Yet, the outcome is irrelevant. Allergists will have to remain physicians—in fact, be physicians rather than allergists—since allergic disease is, as a rule, not the result of immune mechanisms as such, but of the wide range of nonspecific regulations which are superimposed on, and modify immune mechanisms.

One is inclined to concede that today's practice of allergy differs from yesterday's. How real, how fundamental is the difference? It must be insignificant, compared with the advances which we witness in our laboratories. Allergy might represent one of Linus Pauling's "molecular" diseases or, as we used to say, an inborn error of metabolism. Allergic diseases might be caused by the ineffective barrier of the "atopic" individual against a hostile environment. In practice, whether we use antihistamines, bronchodilators, or corticosteroids, we still treat allergic diseases at the last link of the chain. It is the saving grace of allergic reactions that they are so often reversible. As soon as we venture one step further, we find ourselves in areas of discussion and dissent; "routine" immunizations are as controversial as "one-shot" therapy. Most of us "immunize." Most of us, I think, agree that the multiple variables which operate in clinical allergy make it often difficult to decide whether credit for clinical improvement should be given to preventive measures, to immunizations, or to symptomatic therapy. The art of allergy which we practice is based on tradition—the joint experience of generations of allergists. Experience, however, is only the beginning; the art of allergy must now be persuaded to adopt and perhaps to be altered by its own unruly offspring, the science of allergy.

The climate of transition is not limited to the small islands of allergists and allergy; more than the practice of allergy, the world in which we practice it has changed. The relationship between physician and patient—spelled out by the Egyptians, confirmed by Hippocrates, and unmoved by Harvey and the advent of experimental medicine—is on trial. How many years have gone by since the physician's, the healer's word was gospel to be accepted on faith? Today the media of mass communication have placed themselves firmly between us and

our patients. The patient, disturbed and alarmed by a measure of knowledge, is unwilling to be treated by decree; he questions and doubts. Moreover, he feels that we owe him an explanation of our advice. His emotions, on the other hand, are the same as they were at the beginning of time; he might be inquisitive, but he wants primarily help, or perhaps he wants us to perform a miracle which will restore him to the healthy carelessness of youth. The evolution of the patient cannot be undone; it is part of the dynamics of the society in which we live. We might as well abandon the hope for an easy solution, for a sudden clearing of the darkness in the forest. "These are not," Abraham Lincoln said, "the days of miracles, and I suppose it will be granted that I am not to expect a direct revelation. I must study the plain physical facts of the case, ascertain what is possible, and learn what appears to be wise and right. The subject is difficult, and good men do not agree."

The moment of inquiry, the expectant silence in our offices or at the bedside, makes us kinsmen to Jamar, Benos, Herxheimer, and Findeisen. Each one of us is one. In the lead article of last year's midsummer *Atlantic Monthly*, Edward Weeks,* concerned with the increasing inroads and pressures of bigness on man's freedom, asks: "How Big Is One?" and concludes:

> One is as big as Ralph Bunche and Eleanor Roosevelt.
>
> One is as big as Louis M. Lyons, whose interpretation of the news and whose judgment of the popular press have provided, in the words of the Lauterbach Award, "a conscience for a whole profession."
>
> One is as big as I. I. Rabi, a brilliant scientist and a passionate humanist, who, on being asked how long it would take to catch up to Russia and to safeguard our long-range future, replied, "A generation." "You know how long it takes to change a cultural pattern. The growing general awareness of this need will help us, but nevertheless we will have to work hard to succeed in a generation."
>
> One is as big as Frederick May Eliot, president for twenty-one years of the American Unitarian Association, who worked himself to the bone for the deepening of faith for reconciliation.
>
> One is as big as you yourself can make it.

Caught in the trap between the day's work and the vision of a future which promises so much more, it is at times tough and tiresome to keep our feet on the ground when we are drawn to the signs and portents on the horizon. We are doing it, I propose, reasonably well; more so, the tension between our doings and our dreams provides us with ample energy for research. This is no grounds for despair; it is difficult to face a child who has developed progressive pulmonary emphysema, but it is just as difficult to face a child who suffers from leukemia, in the certain knowledge that the control of either is within reach. We are constantly aware of our shortcomings, but our lot—to exist in and yet stand up against the imperfections of life—is not ours alone. It is the impossible of which Cozzens** speaks in the final paragraph of "The Just and the Unjust":

> "Don't be cynical," Judge Coates said. "A cynic is just a man who found out when he was about ten that there wasn't any Santa Claus, and he is still upset. Yes, there will

*Weeks, Edward: How Big Is One? Atlantic Monthly, 1958 (by permission of the author).

**Cozzens, James Gould: The Just and the Unjust, New York, 1950, Harcourt, Brace, and Company, Inc. (by permission of the publisher).

be more wars; and soon, I don't doubt. There always have been. There will be death and disappointments and failures. When they come, you meet them. Nobody promises you a good time, or an easy time. I don't know who it was who said when we think of the past, we regret, and when we think of the future, we fear. And with reason. But no bets are off. There is the present to think of, and as long as you live, there always will be. In the present, every day is a miracle. The world gets up in the morning and is fed and goes to work, and in the evening it comes home, and is fed again and perhaps has a little amusement and goes to sleep. To make that possible, so much has to be done by so many people that, on the face of it, it is impossible. Well, every day, we do it; and every day, come hell, come high water, we're going to have to go on doing it as well as we can."

"So, it seems," said Abner.

"Yes, so it seems," said Judge Coates, "and so it is, and so it will be. And that's where you come in. That's all we want of you." Abner said: "What do you want of me?" "We just want you to do the impossible," Judge Coates said.

The impossible, then, is here to stay, but the impossible has its rewards. Our life is curiously divided. Paul Valéry, I believe, has said that only the extremes of life make life worth living but that only the durable terrain between the extremes sustains it. The administrative ease of the presidency of the American Academy of Allergy relies on the steadiness of the daily conduct of its affairs (or, translated into practical terms, on the effectiveness of the Executive Office), the foundation for the lofty highlands of elation and grandeur.

The wind which blows on the heights is not the wind of security. "On the whole, Whitehead said, "the great ages have been unstable ages." Allergy has changed, and allergists change; it seems likely, and there is already some evidence of it here and there, that the American Academy of Allergy will have to adjust to a world which transforms through radio and television one voice into a million voices, which makes distances meaningless, which refuses to consider the sky the final frontier. Our basic function will remain the same: the American Academy of Allergy is a political body—not only in the practical sense that it governs and regulates but in Plutarch's meaning which defines politics as a way of life. Our political responsibility, however, is only one, and perhaps not the most important, of our commitments. In a peculiar synergism, organizations develop a potential which exceeds by far the added potential of their individual members. Even Emerson who, in "Society and Solitude," leans so subtly toward solitude has found at least "one man to whom no weight of adverse experience will make it for a moment appear impossible that thousands of human beings might exercise towards each other the grandest and simplest sentiments." I like to think of the Academy with the clear-headedness of William Allen White, who knew man to be strong and mean, weak and bewildered, and yet recognized the hidden grace in each of them. If they work side by side "a pattern of social conduct emerges, strange and full of friendly purpose. They who seem to be pulling and hauling, jostling and clamoring, have done a day's work that is somehow good. But they only are as competent and wise as they are free. So the wisdom of kindness—let us call it the love of man—comes to bless the labor."*

*From White, William Allen: The Changing West, New York, The Macmillan Company (by permission of the publisher).

When one of my friends gave me a copy of Fielding's *Tom Jones,* he said: "I know that you will enjoy the book which I read many years ago. I wish I were in your place, considering all of the pleasures which are waiting for you." Likewise, I envy Frank Lowell the term of office which is ahead of him. I am wishing him well, with the relaxed conviction of William Henry Welch, who had finally found a successor for the presidency of Johns Hopkins University: "He seems just the man for us," Welch wrote, and went on to say at the end of his note, "I sang my swan song—as the paper says—at our Commencement yesterday—and I shall get back to my ordinary routine."* I have sung mine and, between regret and relief, it was a wonderful year.

*From Flexner, S., and Flexner, J. T.: William Henry Welch and the Heroic Age of American Medicine, New York, 1941, The Viking Press (by permission of the publisher).

ANNOUNCEMENTS

Northwestern University

Northwestern University Medical School offers a fellowship in allergy beginning about July 1, 1960 (or earlier). The following types of candidates will be considered: (1) those who have had two years of residency in internal medicine or pediatrics, (2) those who have completed their formal training requirements for these Boards, and (3) those who have completed their formal allergy training or experience and desire a period with special emphasis on investigative problems. The stipend is $3,600.00 to $5,000.00, depending on family status and educational background.

Inquiries should be addressed to Samuel M. Feinberg, M.D., Northwestern University Medical School, 303 E. Chicago Ave., Chicago 11, Illinois.

Pittsburgh Allergy Society

At a recent meeting the Pittsburgh Allergy Society elected the following officers for 1959-1961:

President, Macy I. Levine, M.D.
Secretary-Treasurer, Irwin A. Solow, M.D.

American Society of Mechanical Engineers

The American Society of Mechanical Engineers Task Group on Research in Air Pollution is again undertaking a compilation of active air pollution research projects.

The inventory will consist of reservoir projects which were active during 1959 and will include the organization and the researcher.

All organizations and personnel who wish to be included should communicate with Mr. Austin Heller, Chairman, Task Group—Air Pollution Research, American Society of Mechanical Engineers, 29 West 39th St., New York 18, New York.

OBITUARY

DAVID MC KOWEN PIPES

DAVID MC KOWEN PIPES of Baton Rouge, Louisiana, died on Aug. 25, 1959, following a long illness.

Dr. Pipes was born in Jackson, Louisiana, in 1905. He received his A.B. degree from Southwestern Presbyterian University in Memphis in 1928 and his M.D. degree from Tulane Medical School in 1934. Following internship at the Highland Sanitarium in Shreveport, Louisiana, Dr. Pipes served a preceptorship in allergy with Dr. Warren Vaughan in Richmond, Virginia. He practiced allergy in Asheville, North Carolina, for several years prior to moving to Baton Rouge in April, 1958.

Dr. Pipes was elected a member of the Academy in 1940; he was a Fellow of the American College of Allergists and a Fellow of the International Association of Allergists. He was a member of the staff of the Baton Rouge General Hospital.

Dr. Pipes was married in 1955 to Novie Whitmire, who survives him.